

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022328Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

1.3. Administrative Information

PATENT CERTIFICATION

There are no unexpired patents listed in the publication, *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) for the reference listed drug Ambien® (zolpidem tartrate) Tablets, NDA No. 19-908. Accordingly, pursuant to 21 CFR § 314.50(i)(1)(i)(A)(2), Transcept Pharmaceuticals, Inc. (Transcept), submits the following certification:

In the opinion and to the best knowledge of Transcept there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.



Nikhilesh Singh, M Pharm, PhD
Vice President, Chief Scientific Officer
Transcept Pharmaceuticals, Inc.



Date

EXCLUSIVITY SUMMARY

NDA # 22328

SUPPL #

HFD # 120

Trade Name Intermezzo

Generic Name zolpidem tartrate sublingual 1.75 and 3.5 mg tabs

Applicant Name Transcept Pharma., Inc.

Approval Date, If Known 11/ 23/11

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505 b2

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

YES NO

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

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

d) Did the applicant request exclusivity?

YES NO

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

3 years

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

YES NO

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

Not for this formulation, but yes for the reference drug via PWR - Ambien 19908

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA# 19908

Ambien 5 and 10 mg oral tabs

NDA#

NDA#

2. Combination product.

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

YES NO

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

NDA#

NDA#

NDA#

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

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

The efficacy review focused on the two pivotal trials, ZI-06-010, and ZI-12 submitted in support of this application:

Investigation #1: ZI-06-010 – “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” ; N = 82

Investigation #2: ZI-12 – “A Randomized, Double-blind, Placebo-controlled, Crossover Study of the Efficacy and Safety of TransOral Zolpidem in Adult Patients with Insomnia Characterized by Difficulty Returning to Sleep after Middle-of-the-Night (MOTN) Awakening” ; N = 295

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

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

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

Investigation #1	YES	NO X
Investigation #2	YES	NO X

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

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

Investigation #1 YES NO X

Investigation #2 YES NO X

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

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

Investigation #1: ZI-06-010
 Investigation #2: ZI-12

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

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

Investigation #1 !
 !
 IND # 69209 YES X ! NO
 ! Explain:

Investigation #2 !
 !
 IND # 69209 YES X ! NO
 ! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not

identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

N/A

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

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

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

YES NO X

If yes, explain:

=====
Name of person completing form:
Cathy Michaloski (input from Chris Breder, MD, PhD)
Title: RPM
Date: 11/22/11

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

APPEARS THIS WAY ON ORIGINAL



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
11/29/2011

RUSSELL G KATZ
11/29/2011

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

DA/BLA#: 22328 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____
Division Name: DNP PDUFA Goal Date: 11/23/11 Stamp Date: _____
Proprietary Name: Intermezzo
Established/Generic Name: zolpidem tartrate
Dosage Form: 1.75 mg and 3.5 mg sublingual (SL) tablets
Applicant/Sponsor: Transcept Pharma Inc.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
(2) _____
(3) _____
(4) _____

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

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

Indication: middle of the night insomnia (as needed)

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

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

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

- Yes. Please proceed to Section D.
 No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

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

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

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

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

Q3: Does this indication have orphan designation?

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

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

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

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

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

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

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

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

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

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

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

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input checked="" type="checkbox"/>	Neonate	0 wk. __ mo.	__ wk. 72 mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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

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

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

Not feasible:

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

* Not meaningful therapeutic benefit:

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

† Ineffective or unsafe:

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

Δ Formulation failed:

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

Justification attached.

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

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

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

Deferrals (for each or all age groups):			Reason for Deferral			Applicant Certification †
			Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum				
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/> Other	6 yr. __ mo.	16 yr. 11 mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): 3 studies – different due dates						

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

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

* Other Reason: _____

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

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

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

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

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

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

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

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

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

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

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

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

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or

existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

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

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

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

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

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

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

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

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

This page was completed by:

{See appended electronic signature page}

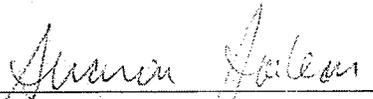
Regulatory Project Manager

(Revised: 6/2008)

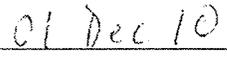
1.3. Administrative Information

DEBARMENT CERTIFICATION

Transcept Pharmaceuticals, Inc. (Transcept), 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.



Sharon Sakai, PhD, RAC
Vice President, Regulatory Affairs
Transcept Pharmaceuticals, Inc.



Date

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

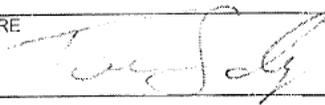
The following information concerning (b) (6), who participated
Name of clinical investigator
as a clinical investigator in the submitted study see attachment
Name of

clinical study _____ is submitted in accordance with 21 CFR part 54. The
named individual has participated in financial arrangements or holds financial interests that are
required to be disclosed as follows:

Please mark the applicable check boxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999, from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest, as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME Thomas P. Soloway	TITLE Sr. Vice President, Operations, & Chief Financial Officer
FIRM/ORGANIZATION Transcept Pharmaceuticals, Inc.	
SIGNATURE 	Date (mm/dd/yyyy) 1/3/2011

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, 420A
Rockville, MD 20850

1 Page has been Withheld in Full as b4
(CCI/TS) immediately following this
page

Michaloski, Cathleen

From: Duvall Miller, Beth A
Date: Monday, November 07, 2011 5:52 PM
To: Michaloski, Cathleen
Cc: Locicero, Colleen L; Nighswander, Robbin M; Bertha, Amy
Subject: NDA 22328 Transcept (Intermezzo) insomnia - cleared for action (again)

Hi Cathy,

We discussed your application at today's clearance meeting and you are cleared for action (again) from a 505(b)(2) perspective.

Other than updating the receipt/PDUFA due date info on your draft assessment, please make sure you also make the changes previously communicated (10/14/09 email below) before archiving in DARRTS.

Thanks,

Beth

Beth Duvall

Team Leader, Regulatory Affairs Team
DER/Office of New Drugs

Direct Phone Number: (301) 796-0513

OND IO Phone Number: (301) 796-0700

Fax: (301) 796-9855

From: Michaloski, Cathleen
Sent: Monday, October 24, 2011 12:46 PM
To: Duvall Miller, Beth A
Cc: Locicero, Colleen L; Nighswander, Robbin M
Subject: RE: NDA 22328 Transcept (Intermezzo) insomnia - cleared for action

Hi Beth,

NDA 22328 was CR's on 7/14/11. Sponsor has re-submitted the NDA and it is a Class 1 re-submission (2 month clock). We hope to take an approval action by Nov 23, 2011. Do we need to obtain another clearance memo from you? Please advise. Thank you.

Cathy

*Cathleen Michaloski, BSN / MPH
Senior Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone 301-796-1123
email: cathleen.michaloski@fda.hhs.gov*



NDA 022328

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Transcept Pharmaceuticals, Inc.
1003 W. Cutting Blvd., Suite 110
Pt. Richmond, California 94804

ATTENTION: Sharon Sakai, PhD, RAC
Vice President, Regulatory Affairs

Dear Dr. Sakai:

Please refer to your New Drug Application (NDA) dated September 30, 2008, received September 30, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zolpidem Tartrate Sublingual Tablets, 1.75 mg and 3.5 mg.

We also refer to your class 1 resubmission dated September 27, 2011, received September 27, 2011.

We also refer to your October 7, 2011, correspondence received October 7, 2011, requesting review of your proposed proprietary name, Intermezzo. We have completed our review of the proposed proprietary name, Intermezzo and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your October 7, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Laurie Kelley, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5068. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Cathleen Michaloski at (301) 796-1123.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CATHLEEN B MICHALOSKI
10/11/2011



NDA 22328

**ACKNOWLEDGE --
CLASS 1 COMPLETE RESPONSE**

Transcept Pharmaceuticals, Inc.
1003 W. Cutting Blvd., Suite 110
Pt. Richmond, CA 94804

Attention: Sharon Sakai, Ph.D., RAC
Vice President, Regulatory Affairs

Dear Dr. Sakai:

We acknowledge receipt on September 27, 2011, of your September 27, 2011, resubmission to your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Intermezzo (zolpidem tartrate) 1.75 mg and 3.5 mg sublingual lozenge (sl) in the treatment of middle of the night (MOTN) insomnia.

We consider this a complete, class 1 response to our July 14, 2011, action letter. Therefore, the user fee goal date is November 27, 2011.

If you have any questions, do not hesitate to contact me at (301) 796-1123.

Sincerely,

{See appended electronic signature page}

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

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/s/

CATHLEEN B MICHALOSKI
10/03/2011



NDA 022328

MEETING MINUTES

Transcept Pharmaceuticals, Inc.
1003 W. Cutting Blvd., Suite 110
Pt. Richmond, CA 94804

Attention: Sharon Sakai, Ph.D.
Associate Director, Regulatory Affairs

Dear Dr. Sakai:

Please refer to your new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Intermezzo (zolpidem tartrate) 1.75 mg and 3.5 mg sublingual lozenge (sl) in the treatment of middle of the night (MOTN) insomnia.

We also refer to the End of Review meeting on September 14, 2011, between representatives of your firm and the FDA, Division of Neurology Products. The purpose of the meeting was to discuss the End of Review of NDA 22328.

A copy of the official minutes of the September 14, 2011 meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Date and Time: September 14, 2011
Meeting Type: End of Review Conference
Meeting Location: White Oak Bldg #22, Room 1309
Application Number: NDA 022328
Product Name: Intermezzo (zolpidem tartrate) for insomnia
Sponsor Name: Transcept Pharma., Inc.
Meeting Requestor: Sharon Sakai, Ph.D.
Meeting Chair: Russell Katz, M.D.
Meeting Recorder: Cathleen Michaloski, BSN, MPH

Meeting Attendees:

FDA CDER Attendees:

Robert Temple, M.D., Director, Office of Drug Evaluation (ODE) I
Ellis Unger, M.D. Deputy Director, ODE I
Russell Katz, M.D., Director, Division Neurology Products (DNP)
Ronald Farkas, M.D. Ph.D., Clinical Team Leader, DNP
Christopher Breder, M.D., Ph.D., Clinical Reviewer, DNP
Angela Men, M.D., Ph.D., Lead Clinical Pharmacology, OTS
Jagan Parepally, Ph.D., Clinical Pharmacology Reviewer, OTS
(b) (4)
Tristan Massie, Ph.D., Mathematical Statistician Reviewer, OTS
Kun Jin, Ph.D., Lead Mathematical Statistician, OTS
Cathleen Michaloski, BSN, MPH, Sr. Regulatory Project Manager, DNP

Sponsor Attendees:

Sharon Sakai, Ph.D., RAC, Vice President, Regulatory Affairs

Glenn Oclassen, President and CEO

Frank Steinberg, D.O., Acting Chief Medical Consultant

Nikhilesh Singh, MPharm, PhD, Vice President and Chief Scientific Officer



1.0 Background and Discussion

The purpose of this meeting was to review the Sponsor's response to the Complete Response Letter dated July 14, 2011. The specific question for this meeting was in reference to decreasing the recommended dose in females to 1.75 mg and revising the dosing instructions to assure that the MOTN dose is [REDACTED] (b) (4)

The meeting discussion was in open format. There was one question in the meeting package. The Sponsor was sent the preliminary response to the question the day prior to the meeting.

Sponsor Question:

1. Transept has proposed that reducing the recommended dose for women to 1.75 mg, and revising the dosing instructions to [REDACTED] (b) (4) [REDACTED] for all patients addresses the Agency's remaining concerns about risks of next-day impairment. Does the Agency agree that the proposed dose [REDACTED] (b) (4) recommendations, which are supported by existing data, adequately address the safety concerns precluding approval of Intermezzo?

DNP Preliminary Response:

We generally agree with your proposal, and believe that if your Complete Response is adequately concise in summarizing morning zolpidem levels and evidence that the levels are safe given this labeling, we may be able to consider the Complete Response a Class 1 resubmission (as described in Guidance for Industry: Classifying Resubmissions in Response to Action Letters, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079303.pdf>).

Meeting Discussion:

There was agreement that the Sponsor would submit a Complete Response that could stand alone, independent of the Briefing Package for this meeting. Specifically, the Sponsor would succinctly summarize their 3, 4, and 5 hr Clinical Pharmacology and Safety data for the 3.5 and 1.75 mg dose groups. This data should be summarized in tabular form and the raw data sent as well. In their characterization of the PK data, the Sponsor should particularly describe the demographics of subjects with higher plasma levels.

The Division raised the concern that the variability of plasma levels in African American men might indicate that rare individuals exist in the population (both African American and other populations) who develop substantially higher than expected zolpidem levels. This was discussed as a possible question to address post-marketing.

2.0 Other Important Information

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

3.0 Action Items/Issues Requiring Further Discussion: None

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/s/

RUSSELL G KATZ
09/28/2011



NDA 022328

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Transcept Pharmaceuticals, Inc.
Attention: Sharon Sakai, PhD, RAC
Vice President, Regulatory Affairs
1003 W. Cutting Blvd., Suite 110
Pt. Richmond, CA 94804

Dear Dr. Sakai:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Intermezzo (zolpidem tartrate) sublingual lozenge.

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).¹ The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or “prep” runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

¹ These violations include studies conducted by Bioassay Laboratories and BA Research International specific to the Houston, Texas facility.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have questions, contact your designated Regulatory Project Manager, at (301) 796-2250.

Sincerely,

{See appended electronic signature page}

Russell G. Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

JACQUELINE H WARE

09/15/2011

Signed for Dr. Russell G. Katz



NDA 022328

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Transcept Pharmaceuticals, Inc.
1003 W. Cutting Blvd., Suite 110
Pt. Richmond, California 94804

ATTENTION: Sharon Sakai, PhD, RAC
Vice President, Regulatory Affairs

Dear Dr. Sakai:

Please refer to your New Drug Application (NDA) dated September 30, 2008, received September 30, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zolpidem Tartrate Sublingual Tablets, 1.75 mg and 3.5 mg.

We also refer to your class 2 resubmission dated January 14, 2011, received January 14, 2011.

We also refer to your March 1, 2011, correspondence received March 1, 2011, requesting review of your proposed proprietary name, Intermezzo. We have completed our review of the proposed proprietary name, Intermezzo and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your March 1, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Laurie Kelley, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5068. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Cathleen Michaloski at (301) 796-1126.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
05/25/2011

Email sent 5.16.11 2 pm

Good Morning, we have the following comments from our Labeling and packaging reviewer. Please call me if any questions. I will also fax the comments which contain the labels and images for reference. Can you confirm your fax number?

Thank you,
Cathy

A. General Comment

The 30-count cartons contain (b) (4) Medication Guides and (b) (4) 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 (b) (4)

(b) (4) The entire statement is important and

therefore we recommend the entire statement be placed in bold print (b) (4)

(b) (4)

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

The net quantity statement [REDACTED] (b) (4)

[REDACTED] 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, 5-count

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

[REDACTED] (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.

Cathleen Michaloski, BSN / MPH
Senior Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration
ph 301-796-1123
email: cathleen.michaloski@fda.hhs.gov

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CATHLEEN B MICHALOSKI
05/16/2011

From: Michaloski, Cathleen
Sent: Monday, May 16, 2011 3:20 PM
To: 'Sharon Sakai'
Subject: Update on REMS and Med guides NDA 22328

Importance: High

Hi Sharon,

Update on the review of REMS. Please note the following change in policy regarding REMS.

"On January 14, 2011, in your NDA re-submission, you proposed a risk evaluation and mitigation strategy (REMS) for Intermezzo (zolpidem tartrate lozenge) to ensure that the benefits of the drug outweigh the increased risks associated with the sedative-hypnotic class. You proposed that your REMS include a Medication Guide and timetable for submission of assessments of the REMS.

You may be aware that on February 28, 2011, the Food and Drug Administration published a Federal Register notice concerning the availability of a draft FDA guidance entitled "Medication Guides — Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)." In addition to discussing the FDA's policy on Medication Guide distribution, this draft guidance addresses the following two topics related to Medication Guides: the FDA's current thinking regarding when Medication Guides will be required as a component in a REMS program as well as procedures for sponsors to follow to request removal of a Medication Guide from a REMS.

In light of this draft Guidance, we do not think that is not necessary for the Medication Guide to be part of a REMS to ensure that the benefits of Intermezzo (zolpidem tartrate lozenge) outweigh its risks. We do believe, however, that the Medication Guide is still necessary for patients' safe and effective use of Intermezzo (zolpidem tartrate lozenge). The Medication Guide under review is being considered as part of labeling; if the NDA is approved, the Medication Guide would become a part of the approved labeling"

If you have any questions please feel free to call me.
Cathy

Cathleen Michaloski, BSN / MPH
Senior Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration
ph 301-796-1123
email: cathleen.michaloski@fda.hhs.gov

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APPEARS THIS WAY ON ORIGINAL



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CATHLEEN B MICHALOSKI
05/16/2011

Email sent to sponsor – clinical information request
NDA 22328 4/27/11

Sharon,
below is a summary of what we discussed at the midcycle. (Technically speaking there are no Midcycles on re-submission.) We had a midway meeting I would say.

We request the following information:

Drug levels in some patients appear to be significantly higher, and PD effects greater, in some patients compared to others. We would like you to conduct analyses to determine if, and to what degree, individual patient response might be predicted based on demographic or other factors (e.g. as reported by Salva and Costa, Clin Pharmacokinet 29 [3]:142-153, 1995 and by Greenblatt et al., J. Pharmacol Exper Ther 293 [3]:435-443, 2000).

Please analyze data from *all* studies in which PK *or* PD data was collected; do not limit your analysis to studies in which both PK and PD data were collected. Include all studies regardless of the dose or formulation of zolpidem used. Please include in your submission an explanation of which studies were included or excluded in these analyses, and why. Please include other demographic factors in your analysis that might influence PK or PD, such as ethnic group and BMI. We are also interested in how factors known to affect PK, such as age and fed/fasted state, might interact with other baseline factors - e.g. what is the effect of gender specifically in elderly patients?.

We are particularly interested in graphical representation of the data. For each study, we are interested in something like the following:

1. Graphs showing individual patient data over time [note: please show all time points measured, not just 'key' time points]. If both PK and PD data is available for that study, please show both sets of data on a single graph for each patient, to the extent that interpretability is preserved (i.e. for studies with multiple PD endpoints, it may be necessary to make more than 1 graph per patient). For PD data, it is only necessary to show graphs of placebo-subtracted change.
2. Graphs showing average group data over time (e.g. male vs. female), with a box-plot (not just a point) for each group at all time points

measured. To the extent that interpretability is preserved, please include both PK and PD data on the same graph, or on a second graph on the same page.

3. Graphs showing tracings from all patients in a group over time. For example, for gender, show tracings from all patients in the study, with a different 'line appearance' for male vs. female (if this is not visually interpretable, separate graphs on the same page would be acceptable).

4. For continuous baseline factors, such as weight and BMI, please show both a) scatter plots and b) data by cut-points (e.g. quartiles, or if small 'N,' possibly only 2 or 3 subgroups). For baseline factors that might be meaningfully correlated, such as gender and weight, show for groups separately (e.g. blood levels by weight for women separately from blood levels by weight for men).

Summary tables of key PK and PD parameters, as generally outlined in your email of April 22, are acceptable. Please include mean, median, and extreme observations in each table.

If you have any questions feel free to call me,
Cathy

From: Michaloski, Cathleen
Sent: Friday, April 22, 2011 2:33 PM
To: Farkas, Ronald; Davis, Carole
Subject: FW: Clinical Question for 22328

Forwarding and Dr. Sakai has a question about our meeting last week.
Please advise.
Cathy

From: Sharon Sakai [mailto:ssakai@transcept.com]
Sent: Friday, April 22, 2011 11:49 AM
To: Michaloski, Cathleen
Subject: RE: Clinical Question for 22328

Hello Cathleen

An update on the request received earlier this week- we are proceeding with subgroup analysis by gender and body weight for the ZI-05-009 study, as this is the only study in which both PK and PD parameters were collected. The following summary tables will be provided:

- PK by gender and body weight for C_{max} , AUC_{0-inf} , AUC_{0-t} , T_{max} , $T_{1/2}$, C_{4hr}
- Summary table for each of the 5 PD parameters studied at the following time points: pre-dose, 20 min, 60 min, 4 hr

The PD time points of 20 and 60 min were chosen to bracket the C_{max} in this study (approx 37 min), and the PD time point of 4 hours was chosen to reflect time when the individual might first be out of bed, consistent with the proposed labeling for the drug. The expected time frame for submission of these materials is the first week of May.

I also wanted to know if there is any other feedback pending from the mid-cycle review meeting, which I believe was to be held last week?

Thank you, and I hope you have a nice holiday.

-Sharon

From: Michaloski, Cathleen [mailto:Cathleen.Michaloski@fda.hhs.gov]
Sent: Monday, April 18, 2011 7:56 AM
To: Sharon Sakai
Subject: Clinical Question for 22328

Sharon, we have a clinical analysis question and request for information.

"Please analyze in the studies you conducted how demographic factors, such as gender and body weight, affected the PK and PD response to zolpidem, both near C_{max} , and at time points at which the individual might first be out of bed."

Any questions, feel free to call me.
Cathy

Cathleen Michaloski, BSN / MPH
Senior Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration

ph 301-796-1123
email: cathleen.michaloski@fda.hhs.gov

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CATHLEEN B MICHALOSKI
04/26/2011

Email to sponsor 3/29/11 10am

Hi Sharon,

We may not need a tcon today - see what you think. Below are the PLR edits we would like you to correct and then return a clean label within a reasonable period of time (no more than 2 weeks)

1. Highlights : All Caps on INTERMEZZO and the control IV needs to be same size as regular font.

2. Adverse Reactions- Under the clinical trials experience put this statement BEFORE section 6.1:

“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.”

3. If there is a post market section under Adverse Reactions will need the following statement added:

“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.”

4. Under Patient Counseling Information:

Begin with :

See FDA“See FDA-approved patient labeling (Medication Guide)” at very start of section.

Also- The MG will follow the PI; streaming in without a header (but we need to wait on that until after the review is complete).

This is all I was going to discuss on the tcon. Content text changes will be sent under separate cover at a later date when clinical review is complete. If you would still like to discuss I am free at 1 pm EDT. Please let me know. Thank you.

Cathy

Cathleen Michaloski, BSN / MPH
Senior Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration
ph 301-796-1123
email: cathleen.michaloski@fda.hhs.gov

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CATHLEEN B MICHALOSKI
03/29/2011

Email to sponsor 3.11.11 11:50 am

Good Day Dr. Sakai,

We have a few follow-up questions related to the video images we received (Dr. Vuurman's files). Please see below:

1. The example given of "speed too low" is a specific condition of 'slowing down to a stop.' Can a "speed too low" designation be given for lesser decreases of speed, say by 10 or 20 km/hr? Since the patient might drive too slowly as a result of the drug, how can it reasonably be assured that an informative episode of difficulty controlling the car is not being edited out by speed too low? What percentage of a test on average is considered "speed too low," and how many episodes of it occur on average (we note there were zero cases in the tracing you previously sent)?
2. In the 'too dark' artifact, is there an absence of signal from the camera, or is the signal shown on the screen shots really the signal from the camera - it looks like a straight line is inserted (interpolated) into a gap with no data.
3. What kind of interaction occurs between the driving instructor and the subject during the test? What instructions are given, and when? Is there any other conversation permitted? Are any observations made about driver or driving behavior, or 'events' (e.g. subjective evaluation of instructor about use of mirrors before changing lanes, appropriateness of following distance, etc).
4. Does the driving instructor indicate in real-time events that are occurring, like passing, exiting highway, or corrective action that the instructor needs to take?
5. What are examples of an 'other' artifact? how many of these artifacts occur in the average test, both as absolute number and percentage of recorded time?
6. Were there any occurrences of corrective action taken by the instructor in any of the tests? how would these be indicated in the submitted data?
7. What does the lateral position signal look like when the patient drives a) very close to, b) on, or c) a little over the lane line? Did any events like this occur in any of the tests, and if so, how would they be defined and indicated in the submitted data?
8. On the lateral position tracing, where would the lane line be? Is there a way to convert the data to 'distance from lane line'?
9. Is a reflection event deduced only on the basis of the speed and position graphs or is there other video evidence used in the determination?

We look forward to hearing from you. Any questions please call me. Thanks,

Cathy

Cathleen Michaloski, BSN / MPH
Senior Regulatory Project Manager

**Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration
ph 301-796-1123
email: cathleen.michaloski@fda.hhs.gov**

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/s/

CATHLEEN B MICHALOSKI
03/11/2011



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Memorandum of Tcon

Date: Feb. 28, 2011 3:00 – 3:30 pm WO 22 room 4396

To: File NDA 22328 Transcept for Intermezzo (insomnia)

Re: Informal telecon to discuss statistical analysis of driving study ZI-18

Sponsor: Transcept Pharma., Inc.

Product: Intermezzo (zolpidem tartrate, sublingual lozenge)

Participants

Sponsor:

Sharon Sakai, Ph.D., Vice President, Regulatory and Quality, Transcept

Nik Singh, Ph.D., Chief Scientific Officer

Frank Steinberg, M.D., Chief Medical Officer

Sal Rico, Ph.D. Director of Clinical Research

Eric Vuurman, Ph.D., Assistant Professor, Dept. Of Psychopharmacology, University of Maastricht

CDER/DNP:

Ron Farkas, M.D., Ph.D. Clinical Team Leader, DNP

Carole Davis, DO, MPH, Clinical Reviewer

Tristan Massie, Ph.D., Statistician Reviewer

Kun Jin, Ph.D. Team Leader Statistics

Cathy Michalsoki, BSN, MPH, Regulatory Project Manager

Summary Minutes:

Sponsor requested a tcon to more fully discuss the statistical questions that were raised and communicated to them last week. The questions were:

1. Please submit the analysis dataset(s) for the comparative analysis of data in the literature vs ZST driving study ZI-18 as described in report ECA-001. Please also submit the corresponding define file(s) and the relevant programming code that was used to carry out the analysis.

2. Please also submit or identify the location of the original electronic source files for the SDLP endpoint in study ZI-18, i.e., before the removal "data artifacts", as described in 11.4.1 of your clinical study report for study ZI-18. If necessary, convert these requested files to the SAS transport format.

The Sponsor responded by allowing the driving study author, Dr. Vuurman, to fully describe the methodology of the study and the statistical procedures that were applied to the data and explain specifically what data were collected and used in the analysis. There were many questions as to what was meant by “artifact” and subsequent elimination of certain data from the analysis. There was concern that elimination of ‘artifact’ data may bias the results either positively or negatively, especially in a study in which the goal is to show similarity between the groups.

The Division noted the concerns about modifying data without having prespecified the rules for data editing in the protocol or statistical analysis plan. The Division believed that since there are no pre-specified rules pertaining to editing the data prior to the analysis and no such standards in driving studies per se, it asked for more documentation. The sponsor offered to send Dr. Vuurman to FDA on a visit to more fully explain and demonstrate his analysis.

For the time being, it was agreed that sponsor would submit:

1. the SOPs and coding conventions for collecting, editing, and analyzing the driving study data,
2. a graphic display of video data mapping out what data was eliminated, and
3. Ascii files (raw data, i.e., before removal of “artifacts”) in SAS transport format.

The sponsor agreed to send this information in as soon as possible. The call ended.

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/s/

CATHLEEN B MICHALOSKI
03/02/2011

Email information request to sponsor: 2.23.11 2:45 pm

Good Day,

We are reviewing the re-submission and have requests for information from the statistician.

1. Please submit the analysis dataset(s) for the comparative analysis of data in the literature vs ZST driving study ZI-18 as described in report ECA-001. Please also submit the corresponding define file(s) and the relevant programming code that was used to carry out the analysis.
2. Please also submit or identify the location of the original electronic source files for the SDLP endpoint in study ZI-18, i.e., before the removal of "data artifacts", as described in 11.4.1 of your clinical study report for study ZI-18. If necessary, convert these requested files to the SAS transport format.

Any questions please call me.
Cathy

Cathleen Michaloski, BSN / MPH
Senior Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration
ph 301-796-1123
email: cathleen.michaloski@fda.hhs.gov

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/s/

CATHLEEN B MICHALOSKI
02/23/2011



NDA 022328

**ACKNOWLEDGE –
CLASS 2 RESPONSE**

Transcept Pharmaceuticals, Inc.
1003 W. Cutting Blvd., Suite 110
Pt. Richmond, CA 94804

Attention: Sharon Sakai, Ph.D.
Vice President, Regulatory Affairs

Dear Dr. Sakai:

We acknowledge receipt on January 14, 2011 of your January 14, 2011 resubmission of your new drug application submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Intermezzo (zolpidem tartrate) 1.75 mg and 3.5 mg sublingual lozenge (sl) in the treatment of middle of the night (MOTN) insomnia.

We consider this a complete, class 2 response to our October 28, 2009 action letter. Therefore, the user fee goal date is **July 14, 2011**.

If you have any questions, call me at (301) 796-1123.

Sincerely,

{See appended electronic signature page}

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

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/s/

CATHLEEN B MICHALOSKI
01/28/2011



NDA 22-328

GENERAL ADVICE

Transcept Pharmaceuticals, Inc.
Attention: Sharon Sakai, Ph.D., RAC, VP, Regulatory Affairs
1003 W. Cutting Blvd., Suite 110
Pt. Richmond, CA 94804

Dear Dr. Sakai:

Please refer to your September 30, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Intermezzo (zolpidem tartrate) Sublingual Tablet.

We have reviewed your revised proposal dated March 15, 2010 to support changes in drug product packaging. Based on your rationale provided, we agree that one batch of 3.5 mg strength tablets packaged at [REDACTED] (b) (4) is adequate to demonstrate packaging capabilities. We note your commitment to provide a comparison of the [REDACTED] (b) (4) and leak testing results in the resubmission. We also note your commitment to complete validation of the packaging process at commercial scale for both tablet strengths as well as your commitment to add the first three commercial batches for both tablet strengths to the stability program at long-term and accelerated conditions.

If you have any questions, call Don Henry, Regulatory Project Manager, at 301-796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/

RAMESH K SOOD

03/19/2010



NDA 22-328

INFORMATION REQUEST

Transcept Pharmaceuticals, Inc.
Attention: Sharon Sakai, Ph.D., RAC, VP, Regulatory Affairs
1003 W. Cutting Blvd., Suite 110
Pt. Richmond, CA 94804

Dear Dr. Sakai:

Please refer to your September 30, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Intermezzo (zolpidem tartrate) Sublingual Tablet.

We also refer to your submission dated March 1, 2010 and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

- We have reviewed your proposal to demonstrate drug product packaging capabilities using the new, unit-dose container closure system. We find your proposal inadequate. We require production of one batch per tablet strength (1.75 mg and 3.5 mg) using the new, unit-dose container closure system. Based on the projected commercial batch sizes provided in your NDA (1.75 mg tablet (b) (4) blisters; 3.5 mg tablet = (b) (4) blisters), the proposed batch size of (b) (4) satisfies the requirement for pilot scale (1/10 commercial) for the 1.75 mg strength tablet but does not satisfy this requirement for the 3.5 mg strength tablet. The batch manufactured for the 3.5 mg strength tablet should include, at a minimum, (b) (4). Be sure to include in your resubmission a comparison of the (b) (4) conditions.

If you have any questions, call Don Henry, Regulatory Project Manager, at 301-796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief, Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/

RAMESH K SOOD

03/09/2010



NDA # 022328

MEETING MINUTES

Transcept Pharmaceuticals, Inc.
1003 W. Cutting Blvd., Suite 110
Pt. Richmond, CA 94804

Attention: Sharon Sakai, Ph.D.
Associate Director, Regulatory Affairs

Dear Dr. Sakai:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Intermezzo (zolpidem tartrate) 1.75 mg and 3.5 mg sublingual lozenge (sl) in the treatment of middle of the night (MOTN) insomnia.

We also refer to the End of Review meeting on January 20, 2010 between representatives of your firm and the FDA, Division of Neurology Products. The purpose of the meeting was to discuss the End of Review of NDA 22328.

A copy of the official minutes of the January 20, 2010 is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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

Sincerely,

{See appended electronic signature page}

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

Enclosure



FOOD AND DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Date and Time: January 20, 2010 3pm-4pm
Meeting Type: Type A End of Review Conference
Meeting Location: White Oak Bldg #22, Room 1413
Application Number: NDA 22328
Product Name: Intermezzo (zolpidem tartrate) for insomnia
Sponsor Name: Transcept Pharma., Inc.
Meeting Requestor: Sharon Sakai, Ph.D.
Meeting Chair: Russell Katz, M.D.
Meeting Recorder: Cathleen Michaloski, BSN, MPH

Meeting Attendees:

FDA CDER Attendees:

Robert Temple, M.D., Director, Office of Drug Evaluation 1
Russell Katz, M.D., Director, Division Neurology Products (DNP)
Ronald Farkas, M.D. Ph.D., Clinical Team Leader, DNP
Angela Men, Ph.D., Supervisory, Clinical Pharmacology
Wendy Wilson, Ph.D., Chemist, ONDQA
Martha Heimann, Ph.D., Pharmaceutical Assessment Lead, ONDQA
Loretta Holmes, Pharm D., Safety Evaluator, OSE
Jeanne Perla, Ph.D., Risk Analyst, OSE
Shawna Hutchins, BSN, RN, Patient Labeling Reviewer, OSE
Robin Duer, RN, MBA, Patient Labeling Reviewer, OSE
Laurie Kelley, PA-C, Safety Project Manager, OSE
Cathleen Michaloski, BSN, MPH, Sr. Regulatory Project Manager

Sponsor Attendees:

Sharon Sakai, PhD, RAC, Vice President, Regulatory Affairs

Rosy Veliz, RAC, Director, Regulatory Affairs

Glenn Oclassen, President and CEO

Frank Steinberg, DO, Chief Medical Consultant

Nikhilesh Singh, MPharm, PhD, Vice President and Chief Scientific Officer

(b) (4)

The meeting discussion was in open format and did not follow the specific questions in any order. The meeting discussion and minutes are at the end of the document.

Sponsor questions:

1. The Division has stated that “ alternative packaging might markedly decrease the possibility of inadvertently taking a second dose (or perhaps even prevent dosing if the patient has less than 4 hours of sleep remaining) would be useful.” In response, Transcept proposes a new four-element packaging system ([Section 2.2](#)): single Unit-Dose Pouch, Dosing Time Chart, Patient Instructions for Use and a Dosing Time Tool, which Transcept thinks will resolve this concern.
 - a. Does the Agency agree that the Unit-Dose Pouch has the potential to decrease the possibility of inadvertently taking a second dose?
 - b. Does the Agency agree that the proposed four-element packaging system addresses the concerns about inadvertent dosing with less than 4 hours of bedtime remaining?
 - c. Transcept is proposing to evaluate these materials in order to optimize the usage and understanding of patient instructions and the four-element packaging system prior to commercialization. Does the Agency agree that this evaluation, in addition to the four-element packaging system, addresses the Agency’s concerns about inadvertent dosing errors?

2. In the [CRL](#), the Division has suggested that additional data are necessary to clearly establish that Intermezzo[®], when taken as directed, does not unacceptably impair driving ability. Given the additional discussion of residual plasma levels 4 hours after dosing presented in this document ([Section 2.1](#)) as well as the lack of residual effects observed in our clinical development program, Transcept believes that there is adequate assurance that blood/tissue concentrations after final awakening will not result in residual effects.

Transcept is committed to conducting a driving study but proposes [REDACTED] (b) (4)

[REDACTED] The details of the proposed study are discussed in [Section 2.3](#); draft protocol is included as [Appendix A](#).

- a. Does the Agency agree that the study evaluating the effect of Intermezzo[®] on next-day driving impairment [REDACTED] (b) (4)

- b. In order to plan for the conduct of such a study [REDACTED] (b) (4), Transcept requests that the Agency confirm that the following study design parameters are appropriate:
 - i. Does the Agency agree with the timing of the driving assessment which is the time one would drive if taking the medication as indicated?

 - ii. The primary endpoint will be Impaired Drivers, where Impaired Driver (ImpDr) is a binary indicator defined for subject i to be 1 if $\text{TreatmentSDLP}[i] - \text{PlaceboSDLP}[i] > 2.5$ cm and zero otherwise. Does the Agency agree?

 - iii. The definition of impaired driving will be an increase in 2.5 cm, the level of increase associated with a BAC of 0.05. In addition, other cutpoints and approaches will be assayed. Does the Agency agree with the definition of an “impaired driver” and with the additional cutpoints as proposed?

 - iv. Does the Agency agree with the overall statistical approach described in the protocol?

 - v. The study will be conducted in normal volunteers as they represent the most sensitive assay of ‘Impaired Driver’. Does the Agency agree?

 - vi. The active control will be zopiclone 7.5 mg. This is selected as it has been the compound most often studied and consistently produced impairment relative to placebo in these types of studies. Does the Agency agree?

3. Transcept’s resubmission in response to the [CRL](#) will consist of the following elements in total:

- An alternative four-element packaging system: Unit-Dose Pouch, Dosing Time Chart, Patient Instructions for Use and a Dosing Time Tool to minimize risk of inadvertently taking a second dose during the night as well as inadvertently taking a dose with less than 4 hours of bedtime remaining. The usage and understanding of patient instructions and the four-element packaging system will be evaluated prior to commercialization.
- The REMS plan will be updated to reflect the risks of inadvertent redosing or dosing with less than 4 hours of bedtime remaining, including the addition of a Patient Instruction for Use to follow the Medication Guide. The details of the REMS update will be submitted at a later date.
- Additionally, Transcept will commit to conduct [REDACTED] ^{(b) (4)} driving study to confirm that driving performance is not impaired when assessed in the morning following a middle-of-the-night dose of Intermezzo[®] 3.5 mg.
 - a. Does the Agency agree that this proposed resubmission package will provide sufficient assurance of the safe use of Intermezzo[®] to support approval?

MEETING MINUTES

The division stated that the proposed individual-dose packaging appeared, on-face, to decrease concerns about risk of inadvertent re-dosing of Intermezzo. However, the division remained concerned that the sponsor's new risk-mitigation strategies might not adequately address the risk of impaired driving resulting from other dosing errors.

The division considered that a possible way for the sponsor to address concerns about dosing errors would be to conduct a patient-use study prior to approval, to demonstrate that patients could take Intermezzo as directed, particularly in terms of timing of dosing in relation to wake-time. The sponsor proposed a study that would ascertain patient understanding of dosing instructions, but that would not directly observe if patients could follow the instructions. The division expressed skepticism that such a study would provide adequate reassurance of safety. The sponsor argued that a study that attempted to directly observe patient ability to follow dosing instructions would be neither possible nor useful (e.g. because patient behavior would change when under observation). The division agreed to consider the sponsor's arguments in their Complete Response.

The dosing aids were briefly discussed. It was noted that on the wheel-shaped dosing aid the bedtimes and awakening times should seemingly be reversed in position.

The discussion then turned to driving studies. The sponsor expressed skepticism about both the interpretability and sensitivity of driving studies, and proposed that pre-approval psychomotor

studies would adequately demonstrate safety. The division expressed concern that the ability of psychomotor tests to represent driving impairment is not well-established.

The sponsor argued that blood levels of zolpidem from Intermezzo would be no higher than from other zolpidem-containing products, and would not present a driving risk. The division agreed that, when taken as directed, blood levels of zolpidem from Intermezzo were not higher than other marketed products, but the division stressed that the as-needed, middle-of-the-night dosing of Intermezzo potentially increased risk of dosing error and consequent higher morning levels.

The division suggested that the sponsor study driving ability at different time-intervals after dosing, but the sponsor argued that studying more than a single time-interval between dosing and driving became impractical. There was discussion of the appropriate comparator/control arm; the most straightforward would be another sleep drug, but this had the shortcoming of only providing relative, not absolute information about driving impairment. It was agreed that the sponsor would provide a proposal for driving studies.

OSE requested that the sponsor submit for review the actual protocol(s) for any patient use study they might propose.

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

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/s/

CATHLEEN B MICHALOSKI
02/18/2010

RUSSELL G KATZ
02/19/2010

Email to Sponsor 2.18.10 1:50pm

Dear Sharon,

Our Med Errors and Prevention Group has the following comments:

**DMEPA's Response to Questions from the Applicant
Intermezzo (Zolpidem Tartrate Sublingual Tablets), NDA 022328**

1. We were pleased to hear that you already have some specific comments on the packaging. You had indicated that you might attach these to the official meeting minutes, but I wanted to let you know that we have further evaluations of the packaging planned for early February, and would therefore find it very helpful if we can get any feedback you might have already as soon as possible. Can you let me know if this is in a form that can be shared with us at this point in time?

From DMEPA's perspective, it is premature at this point to give recommendations since we prefer that any changes made to the packaging be made based on the findings obtained from testing the proposed packaging, labels and labeling.

2. The OSE reviewers were requesting some additional information on the evaluations of the packaging we have done so far. Can you confirm what beyond the moderator guide they might be specifically looking for?

DMEPA would like to see the data you already have in support of the proposed packaging, labels and labeling and the protocols for any testing that you plan to do to further evaluate them. Specifically, we would like to know participant characteristics, the number of participants, the setting, what's being tested, and the plan for addressing any problems with the labels/labeling once identified.

Please let me know if any questions.

Cathy

Cathleen Michaloski, BSN / MPH
Senior Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration
ph 301-796-1123
email: cathleen.michaloski@fda.hhs.gov

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

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/s/

CATHLEEN B MICHALOSKI
02/18/2010

Email sent tot Sponsor 9/4/09

Good Morning Sharon,
below are the safety comments just received last evening from OSE. If you have any questions please feel free to contact me.

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 (b) (4) Using the same color for the trade dress 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. (b) (4)

(b) (4)

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Cathleen Michaloski, BSN / MPH
Senior Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration
ph 301-796-1123
email: cathleen.michaloski@fda.hhs.gov

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

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/s/

CATHLEEN B MICHALOSKI
09/04/2009
safety labels comments email

INTEROFFICE MEMORANDUM

TO: INTERMEZZO CLINICAL REVIEW TEAM
FROM: WENDY WILSON, ONDQA REVIEWER
SUBJECT: PROPOSED CHANGE IN DRUG PRODUCT PACKAGING
DATE: 8/11/2009
CC: HEIMANN, MARTHA; SOOD, RAMESH

This memorandum is in response to the request for consultation received August 5, 2009 regarding changes to the proposed commercial drug product packaging being considered by the clinical review team to mitigate potential medication errors.

(b) (4)

Changes to proposed packaging under consideration: individual unit blisters packaged in single, child-resistant foil packets contained in cartons for distribution to patients



Chemistry, Manufacturing, and Control Considerations

Changing the drug product packaging impacts the manufacturing process and drug product stability. Changing the proposed drug product packaging at this stage of development represents a significant change in the manufacturing process as well as a significant burden to the sponsor. Development time will be needed to re-design the container closure system, identify vendors, revise the manufacturing process, establish appropriate controls for the new packaging process and generate supporting stability data to demonstrate stability of the product in the new packaging system.

The sponsor will need to demonstrate that they are capable of packaging the drug product in the individual blisters. If the sponsor is able to develop an individual blister using the same drug product contact material as used for the primary stability batches, we will require production of three batches at commercial scale using the new packaging process. Because the sponsor currently contracts commercial packaging, the validation can focus only on the packaging process. The sponsor will need to conduct leak testing to confirm that the new blister presentation is adequately sealed as well as vapor and light transmission testing to ensure the new blister provides similar protection to the blister used for the primary stability batches. The sponsor will also need to submit updated CMC information for the manufacturing process, container closure system, and batch records. If the new blister configuration uses different materials than those used for the primary stability batches which do not provide same or better protection from the environmental factors such as temperature and humidity, the sponsor will need to conduct at least six months of accelerated and 12 months of long-term stability testing using the new blister based on the proposed drug product expiry of 24 months.

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/s/

WENDY I WILSON
08/11/2009

RAMESH K SOOD
08/11/2009



NDA 22-328

INFORMATION REQUEST LETTER

Transcept Pharmaceuticals, Inc.
Attention: Sharon Sakai, Ph.D., RAC, Sr. Director, Regulatory Affairs
1003 W. Cutting Blvd.
Pt. Richmond, CA 94804

Dear Dr. Sakai:

Please refer to your September 30, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Intermezzo (zolpidem tartrate) Sublingual Tablet.

We also refer to your submission dated July 10, 2009 and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

- Provide a revised drug product stability specification reflecting the agreed-upon revisions to the acceptance criteria for total related substances, (b) (4), and dissolution.

If you have any questions, call Don Henry, Regulatory Project Manager, at 301-796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief, Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Martha Heimann
7/16/2009 09:43:18 AM
Signed for Ramesh Sood



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Memorandum of Tcon

Date: April 22, 2009 12 pm EST

To: File NDA #22328 IND #69209
REMS issues; dosing compliance

Sponsor: Transcept Pharma., Inc.

Product: Intermezzo (zolpidem tartrate) 1.75 mg and 3.5 mg SL tabs (MOTN
Insomnia)

Recorder: Cathleen Michaloski, BSN, MPH

FDA Attendees: Russell Katz, MD (Director), Ron Farkas, MD PhD (Clin Team Leader), Carole Davis, DO (Clinical Reviewer), Jagan Parepally, PhD (Clin Pharm), Alicija Lerner, PhD (Controlled Substances Staff), Nancy Carothers, RN (patient information specialist), Cathy Michaloski, MPH (Project Manager)

Transcept attendees: Sharon Sakai, PhD, RAC (Vice President, Regulatory Affairs), Rosy Veliz, RAC (Director, Regulatory Affairs), Frank Steinberg, DO (Chief Medical Consultant), Nikhilesh Singh, MPharm, PhD (Vice President and Chief Scientific Officer), [REDACTED] (b) (4)

Tcon Meeting Summary: (Sakai and Michaloski)

Dr. Katz opened the meeting by stating that in the review there are possible concerns associated with the dosing regimen (i.e. middle of the night dosing). The sponsor was asked to address this issue and to submit a proposed plan to address this possible risk. Specifically, the issues are as follows:

1. Is there is a possibility that patients may take more than one pill per night? - Can patients reliably judge when they have 4 hours of bedtime remaining? In this context do we have information specifically on when patients actually woke up in relation to taking a pill (what do we know about effects if drug was taken with less than 4 hours remaining)?

2. Concerning the possibility of that amnesia is the mediator of the above listed events and the potential for taking an additional dose: (b) (4) discussed that the probability of amnesic events is known to be dose-related, greater with higher blood levels, and that there would, therefore, be a safety margin associated with the proposed doses of Intermezzo. (b) (4) indicated that a PK-PD study of our product showed that PD effects returned to baseline with 2.5-3 hours after dosing (Study ZI-05-009 in NDA submission, recently published in Hum Psychopharmacol). Dr. Katz asked to confirm that it was a daytime dosing study, and that effects may not be identical after dosing in the middle of the night. (b) (4) indicated that he does not know if there is any evidence for circadian rhythm effect on amnesia or performance impairment (i.e. effects specific to middle of the night awakening).

3. Concerning the question of whether patients can reliably judge when they have four hours of sleep remaining: The Division noted that unlike the outpatient study, a more carefully controlled situation than real-world usage, patients will not be making phone calls seeking permission to dose and indicated that because amnesia with the drug is a concern, medication error is an issue. The Division (Dr. Farkas) also asked whether, in real world usage, patients would follow directions for MOTN dosing? The Division raised the possibility of a “use study”, would patients actually follow a set of instructions? He indicated that the Division had no preconceived notion of what this should look like, but that Transcept should think about this.

5. Concerning specific information on when patients actually woke up, Transcept will evaluate if there is any data concerning this issue and get back to FDA.

(b) (4) asked Dr. Katz if he felt that the concerns about taking more than one pill are hypothetical concerns, and Dr. Katz indicated yes.

Dr. Katz did state that a REMS beyond the Medication Guide will be required. Possible additional items would include educational materials or a survey to track correct usage.

Transcept will prepare a submission to address the concerns raised above.

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/s/

Cathleen Michaloski
7/16/2009 09:40:25 AM
CSO

Cathleen Michaloski
7/16/2009 09:40:57 AM
CSO



NDA # 22328

Extension of User Fee Goal Date

Transcept Pharmaceuticals, Inc.
1003 W. Cutting Blvd., Suite 110
Pt. Richmond, CA 94804

Attention: Sharon Sakai, Ph.D.
Associate Director, Regulatory Affairs

Dear Dr. Sakai:

Please refer to your September 30, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Intermezzo (zolpidem tartrate) 1.75 mg and 3.5 mg sublingual lozenge (sl).

On May 29, 2009, we received your May 29, 2009 major amendment related to your Risk Evaluation and Mitigation Strategy (REMS) for this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is **October 30, 2009**.

In addition, the Division believes that the arguments you submitted with your NDA in support of [REDACTED] (b) (4) however, we request that you submit a list of pediatric studies for patients between the ages of 6 and 17 years, inclusive, that you intend to complete to satisfy PREA requirements. The Division does agree with waiver of PREA studies for patients less than 6 years of age.

If you have any questions, call Cathleen Michaloski, Sr. Regulatory Project Manager, at 301-796-1123.

Sincerely,

{See appended electronic signature page}

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

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/s/

Russell Katz
6/26/2009 11:03:49 AM

Email sent to sponsor 5/6/09 1pm

Hi Sharon,

As we discussed, there are new authorities under FDAAA regarding safety of new drugs. These new requirements were implemented in March 2008. Since your application has a Med Guide, these authorities are automatically triggered.

We could not find the REMS in your application and therefore we address it here.

Please complete the attached form and send back officially under the NDA. This form is a REMS for the Med Guide.

Per our discussions earlier on April 22, 2009, we will expect a well thought out comprehensive plan to address possible problems related to dosing in the middle of the night, as a separate information requirement.

The attached form may also help in addressing those issues.

Please send in the forms under the NDA. If you have any questions please feel free to call me.

Thank you.

Cathy



REMS templ
5.6.09.doc (67 KB)

*Cathleen Michaloski, BSN / MPH
Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration
ph 301-796-1123
email: cathleen.michaloski@fda.hhs.gov*

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/s/

Cathleen Michaloski
5/27/2009 01:39:42 PM
CSO

Cathleen Michaloski
5/27/2009 01:40:16 PM
CSO

Michaloski, Cathleen

From: Michaloski, Cathleen
Sent: Wednesday, May 06, 2009 1:02 PM
To: 'Sharon Sakai'
Subject: NDA 22328 risk evaluation and mitigation strategy (REMS)

Importance: High

Attachments: REMS templ 5.6.09.doc

Hi Sharon,

As we discussed, there are new authorities under FDAAA regarding safety of new drugs. These new requirements were implemented in March 2008. Since your application has a Med Guide, these authorities are automatically triggered.

We could not find the REMS in your application and therefore we address it here.

Please complete the attached form and send back officially under the NDA. This form is a REMS for the Med Guide.

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Please send in the forms under the NDA. If you have any questions please feel free to call me.

Thank you.

Cathy



REMS templ
5.6.09.doc (67 KB)

*Cathleen Michaloski, BSN / MPH
Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration
ph 301-796-1123
email: cathleen.michaloski@fda.hhs.gov*

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/s/

Cathleen Michaloski
5/6/2009 01:23:28 PM
CSO

Cathleen Michaloski
5/6/2009 01:24:01 PM
CSO



NDA 22-328

INFORMATION REQUEST LETTER

Transcept Pharmaceuticals, Inc.
Attention: Sharon Sakai, Ph.D., RAC, Sr. Director, Regulatory Affairs
1003 W. Cutting Blvd.
Pt. Richmond, CA 94804

Dear Dr. Sakai:

Please refer to your September 30, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Intermezzo (zolpidem tartrate) Sublingual Tablet.

We also refer to your submissions dated December 24, 2008, February 6, 2009, March 12, 2009, March 17, 2009, and March 19, 2009.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Explain how you arrived at the designation of the drug substance (b) (4). Provide justification, supported by data, for the exclusion of a drug substance (b) (4) control in the proposed regulatory specification. Provide justification, supported by data, for not classifying drug substance (b) (4) form as a critical quality attribute.
2. We recommend tightening of the proposed drug product regulatory specification with regards to the limits for total related substances, (b) (4), and disintegration time based on batch analysis and stability data. Based on the classification of the drug product as a tablet as well as the drug product release and stability data submitted with your application, we recommend revising your drug product dissolution acceptance criterion to $Q = (b) (4)$ in 15 minutes.
3. Provide a sample, representative of the commercial configuration, of the proprietary (b) (4) packaging component. Provide material of construction information and use instructions for the proposed proprietary (b) (4) packaging component. If not available, provide a letter of authorization granting access to the DMF associated with this secondary packaging component.
4. Provide updated container and carton labels for the (b) (4) that reflect the revised drug product name and trade dress. Include the drug product lot and expiry on the physician sample carton labels and the (b) (4) labels.
5. Information has been requested from the DMF holder for DMF (b) (4) that is referenced in your application.

If you have any questions, call Don Henry, Regulatory Project Manager, at 301-796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief, Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ramesh Sood

5/8/2009 08:09:48 AM



FILING COMMUNICATION

NDA # 22-328

Transcept Pharmaceuticals, Inc.
1003 W. Cutting Blvd., Suite 110
Pt. Richmond, CA 94804

Attention: Sharon Sakai, Ph.D.
Associate Director, Regulatory Affairs

Dear Dr. Sakai:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for zolpidem tartrate sublingual tablet for the treatment of insomnia.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Standard**. Therefore, the user fee goal date is **July 30, 2009**.

We request that you submit the following information:

Chemistry, Manufacturing and Controls Comments

1. The acceptance specification for zolpidem tartrate drug substance references European Pharmacopeia (EP) procedures for assay, color of solution, and clarity of solution. Provide copies of the referenced EP analytical procedures.
2. The application contains a stability commitment for post-approval batches (i.e., the first three commercial batches per strength) and annual stability batches, and the stability test protocol for annual batches. The stability protocol for the post-approval commercial batches was not included. Revise the stability commitment to include the stability protocol for the first three post-approval commercial batches.
3. Based on our review of the information provided in your NDA submission, the drug product does not [REDACTED] (b) (4)

Pharmacology / Toxicology Comments

Regarding Study RYN00001 (“A 28-Day Cheek Pouch Local Tolerance Study of ST Zolpidem in Hamsters with a 14-Day Recovery Period”) submitted in serial 055 dated 11/12/07, please provide the following:

- Summary tables for the histopathology assessments that include both the incidence and severity for the microscopic findings; for severity scores, please provide both means and ranges.
- An explanation for the apparent discrepancy between observed clinical signs (e.g., “open lesion around mouth”) and the lack of similar findings postmortem in 1HDM and 3HDF in the abrasion phase.

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

Required Pediatric Assessments

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a [REDACTED] (b) (4)

The waiver is sought and based, in part, on data submitted to the Agency included in the Ambien® (zolpidem tartrate) pediatric efficacy supplement 022, where administration of zolpidem tartrate to attention-deficit/hyperactivity disorder (ADHA) children ages 6-17 years did not establish efficacy and showed significant safety concerns in the pediatric age group listed above. Once we have reviewed your request, we will notify you if the [REDACTED] (b) (4) [REDACTED] and if a pediatric drug development plan is required.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

Russell Katz
12/11/2008 04:59:39 PM



NDA 22-328

NDA ACKNOWLEDGMENT

Transcept Pharmaceuticals, Inc.
1003 W. Cutting Blvd., Suite 110
Pt. Richmond, CA 94804

Attention: Sharon Sakai, Ph.D.
Associate Director, Regulatory Affairs

Dear Dr. Sakai:

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

Name of Drug Product: **Intermezzo (zolpidem tartrate lozenge) sublingual
1.75 mg and 3.5 mg**

Date of Application: **September 30, 2008**

Date of Receipt: **September 30, 2008**

Our Reference Number: **NDA 22-328**

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on **November 29, 2008** in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

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

Food and Drug Administration
Center for Drug Evaluation and Research

Division of Neurology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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

If you have any questions, call me at (301) 796-1123.

Sincerely,

{See appended electronic signature page}

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

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/s/

Cathleen Michaloski
10/24/2008 04:42:11 PM