

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022328Orig1s000**

**CHEMISTRY REVIEW(S)**

# MEMORANDUM

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

**DATE:** October 20, 2011

**FROM:** Lyudmila N. Soldatova, Ph.D., ONDQA/DNDQA I

**SUBJECT:** **CMC Evaluation of CR dated 27-Sep-2011 (Class 1 Resubmission) of NDA 22-328 for Intermezzo (zolpidem tartrate) Sublingual Tablets, 1.75 mg and 3.5 mg**

## Background

The Quality recommendation for NDA 22-328 resubmission dated 14-Jan-2011 was Approval (CMC Review #2 by Lyudmila Soldatova, dated 10-May-2011). The overall Acceptable OC recommendation for drug substance and drug product facilities was received on 29-Apr-2011. Regarding the updated 4-element packaging system for Intermezzo® tablets, the new proposed system was found acceptable from the CMC standpoint. The 24 months expiry was granted for the commercial drug product, 1.75 mg and 3.5 mg dosage strengths, packaged in the proposed single unit dose foil/foil blister/single unit dose pouch configuration, and stored at USP controlled room temperature, protected from moisture.

The new CR Letter dated 14-Jul-2011 was issued by Division of Neurology Products. The Class 1 resubmission was filed by the applicant on 27-Sep-2011.

## Evaluation

From the CMC standpoint, the recommendation remains **Approval** for the NDA 22-328 Resubmission dated 27-Sep-2011. No new CMC information was filed in this resubmission. The Approval recommendation is based on the Approval status of the previous NDA resubmission, and on the statement from OC that all of the facilities listed in the original application for NDA 22-328 are current (as per Compliance Officer Shawn Gould's message dated 06-Oct-2011). The OC re-evaluation date is 24-Mar-2013. The updated labeling (the Description Section of the PI insert) was suggested for DNP on 17-Oct-2011. The updates are: (1) editing the recommendation for use to "Intermezzo sublingual tablets are intended to be placed under the tongue where they will **disintegrate** in (b) (4)", and (2) replacing the chemical name to USAN name *N,N*-6-trimethyl-2-*p*-tolylimidazo[1,2- $\alpha$ ]pyridine-3-acetamide L-(+)-tartrate (2:1) to keep consistency with the labeling for reference drug Ambien®.

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/s/  
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LYUDMILA N SOLDATOVA  
10/20/2011

RAMESH K SOOD  
10/20/2011

**NDA 22-328**

**Zolpidem Tartrate Sublingual Tablet**

**Transcept Pharmaceuticals, Inc.**

**Lyudmila N. Soldatova, Ph.D.**  
**Office of New Drug Quality Assessment**  
**for**  
**Division of Neurology Drug Products**

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1. NDA: 22-328
2. REVIEW: #2
3. REVIEW DATE: 03-MAY-2011
4. REVIEWER: Lyudmila. N. Soldatova, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Review #1	30-JUL-2009

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
NDA Re-submission	14-JAN-2011
Amendment	08-MAR-2011

7. NAME & ADDRESS OF APPLICANT:

Name: Transcept Pharmaceuticals, Inc.  
Address: 1003 W. Cutting Blvd., Suite 110  
Pt. Richmond, CA 94804  
Representative: Sharon Sakai, Ph.D., RAC  
Vice President, Regulatory Affairs  
Telephone: 510-215-3515

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Intermezzo® (proposed)
- b) Non-Proprietary Name (USAN): Zolpidem Tartrate
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):

## Chemistry Review Data Sheet

- Chem. Type: 3
- Submission Priority: S

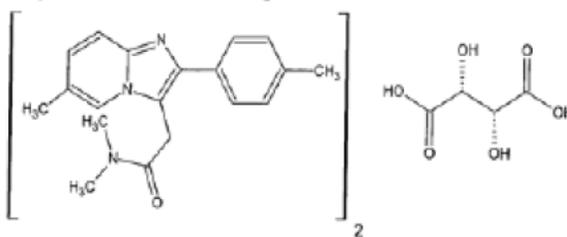
9. LEGAL BASIS FOR SUBMISSION: 505 (b)(2)
10. PHARMACOL. CATEGORY: Insomnia following middle-of-the-night waking
11. DOSAGE FORM: Tablet
12. STRENGTH/POTENCY: 1.75 mg, 3.5 mg
13. ROUTE OF ADMINISTRATION: Sublingual
14. Rx/OTC DISPENSED:  Rx  OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):  
 SPOTS product – Form Completed  
 Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: N,N-6-trimethyl-2-p-tolylimidazo[1,2- $\alpha$ ]pyridine-3-acetamide L-(+)-tartrate (2:1)

Mol. Weight: 764.89

Mol. Formula: C<sub>42</sub>H<sub>48</sub>N<sub>6</sub>O<sub>8</sub>



Chemistry Review Data Sheet

**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	4	N/A		
	III			4	N/A		
	II			3	Adequate	21-APR-2011	Reviewed for ANDA

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no relevant revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

**18. STATUS:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	29-APR-2011	A. Inyard
DMEPA	Pending		Loretta Holmes

# The Chemistry Review for NDA 22-328

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From the CMC standpoint, we recommend Approval of the NDA 22-328 for Intermezzo® (Zolpidem Tartrate) Sublingual Tablets, 1.75 mg and 3.5 mg strengths. The overall Acceptable OC recommendation for drug substance and drug product facilities is received on 29-Apr-2011. Regarding the updated 4-element packaging system for Intermezzo® tablets, the new proposed system is acceptable from the CMC standpoint. The 24 months expiry could be granted for the commercial drug product, 1.75 mg and 3.5 mg dosage strengths, packaged in the proposed single unit dose foil/foil blister/single unit dose pouch configuration, and stored at USP controlled room temperature, protected from moisture.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None as per this review.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

Zolpidem tartrate sublingual tablets are uncoated, biconvex-shaped, and debossed with ZZ on one side. The reverse side is blank. The manufacturer supplies two strengths of drug product, 1.75 mg, and 3.5 mg. The 1.75 mg strength is yellow and the 3.5 mg strength is beige. For each strength, the sublingual tablet weight is 210 mg. For manufacture, description and composition of the drug product refer to the Review #1 for this NDA dated 30-Jul-2009. The proprietary name Intermezzo® was resubmitted by the applicant for Agency evaluation.

The API of the Intermezzo® sublingual tablets, Zolpidem tartrate, is a Schedule IV controlled substance; it is a non-benzodiazepine hypnotic agent of the imidazopyridine class of drugs. Zolpidem tartrate has a water solubility of 23 mg/ml and has been shown to have oral bioavailability of 70%.

The subject of the resubmission of this NDA is a proposal for newly developed unit-dose, 4-element packaging system for Intermezzo® tablets. The new packaging system was developed in response to the Agency's safety concern about inadvertent medication errors that might be associated with middle-of-the-night dosing and proposed initially container closure systems (Complete Response Letter dated October 28-Oct-2009). The new system is proposed to be used to limit bedside access to a single dose of the tablets. The 4-element packaging system consists of the single unit dose foil/foil blister packaged individually in the single unit dose pouch, patient's instruction for use, and dosing wheel. For blister trade packages, thirty unit-dose

## Executive Summary Section

pouches will be packaged in a carton, and for physician samples a single-unit pouch will be packaged into a single-unit carton. Based on the information provided by Transcept Pharmaceuticals, Inc. (Transcept), the proposed blisters for commercial product are comparable to the blisters used for registration batches, and, therefore, the stability results from the registration batches in the original NDA are applicable to the commercial drug product. The applicant has provided the additional 36-month stability data for registration batches that support an expiry of 24 months (established in the Review #1 dated 30-Jul-2009, and claimed by the applicant in this re-submission) for the commercial drug product packaged in the proposed new single unit dose foil/foil blister configuration, and stored at USP controlled room temperature, protected from moisture. The new packaging process will be performed at the (b) (4) (b) (4), a different packaging facility that that used for packaging in the original NDA.

**B. Description of How the Drug Product is Intended to be Used**

Transcept has developed the zolpidem tartrate sublingual tablets, 1.75 mg and 3.5 mg, for the as needed treatment of insomnia characterized by difficulty returning to sleep after awakening in the middle of the night (MOTN).

The proposed Intermezzo® sublingual tablets administration is outlined in the proposed Package Insert below:



## Executive Summary Section

**C. Basis for Approvability or Not-Approval Recommendation**

We recommend Approval of the re-submitted NDA 22-328 for Intermezzo® (Zolpidem Tartrate) Sublingual Tablets, 1.75 mg and 3.5 mg strengths. The newly developed 4-element packaging system for Intermezzo® tablets is acceptable from the CMC standpoint. The overall Acceptable OC recommendation for drug substance and drug product manufacturing facilities is received. The labeling provides adequate information on the storage, expiry, ingredient, and how supplied.

**III. Administrative****A. Reviewer's Signature**

Electronic signature

**B. Endorsement Block**

Chemist Name: Lyudmila Soldatova  
Chemistry CMC Lead: Martha Heimann  
Chemistry Branch Chief: Ramesh Sood

**C. CC Block**

Chemistry Project Manager: Teshara Bouie  
Clinical Project Manager: Cathleen Michaloski

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LYUDMILA N SOLDATOVA  
05/10/2011

RAMESH K SOOD  
05/10/2011

**Intermezzo**  
**(zolpidem tartrate) sublingual tablets**  
**NDA 22-328**

**Summary Basis for Recommended Action**  
**From Chemistry, Manufacturing, and Controls**

**Applicant:** Transcept Pharmaceuticals Inc.  
Pt. Richmond, CA 94804

**Indication:** Indicated for the treatment of insomnia after middle of the night waking.

**Presentation:** Intermezzo (zolpidem tartrate) sublingual tablets are uncoated, biconvex shaped tablets, debossed with ZZ on one side. The tablets are available in two strengths, 1.75 mg (yellow) and 3.5 mg (beige). The tablets will be available in (b) (4) child resistant compliance package. The tablets are moisture sensitive and should be protected from moisture.

**EER Status:** Acceptable, 1-Jun-09

**Consults:** ONDQA Biopharmaceutics : none  
Methods Validation – Revalidation by Agency was not requested.  
EA – Categorical exclusion granted under 21 CFR §25.31(c).

**Post-Approval Agreements:** None

## **II. Summary of Chemistry Assessments**

### **A. Description of the Drug Product(s) and Drug Substance(s)**

#### **Drug Substance:**

Zolpidem tartrate is a white to almost white, hygroscopic, crystalline powder that is slightly soluble in water, sparingly soluble in methanol, and practically insoluble in methylene chloride. The drug substance used for manufacturing the product exists as (b) (4). The CMC information for the drug substance has been referenced to DMF (b) (4). The drug substance is manufactured by (b) (4). The DMF was found to be adequate to support this NDA. The drug product manufacturer tests all incoming batches of the drug substance to ensure that they meet the acceptance specification. The drug substance acceptance specification includes tests and acceptance criteria for description, identification (IR), (b) (4) appearance of solution, pH, heavy metals, water, residue on ignition, assay, tartrate content, related substances, residue on ignition and particle size.

All analytical methods have been adequately validated for their intended use.

**Conclusion: Acceptable.**

**Drug product:**

The drug product is designed as a sublingual tablet. This is a schedule IV product. The identity and quality of the inactive ingredients used in the product is ensured either through their conformance to the USP/NF monographs or through firm's internal specification. The tablets have a constant weight for both strengths. Intermezzo® manufacturing involves (b) (4)

The drug product quality is controlled through appropriate in-process controls and final product specification. The drug product specification includes tests and acceptance criteria for appearance, identification (HPLC/UV), dissolution, disintegration, related substances (HPLC), assay (HPLC), pH, uniformity of dosage form by content uniformity and microbial limits. All analytical procedures used for the analysis are appropriately validated. The commercial product will be packaged in (b) (4) foil/foil blisters. (b) (4)

An expiration period of 24 months is being assigned to this product based on the submitted stability data when stored in the commercial packaging system at room temperature.

**Overall conclusion:** The application is recommended for approval from CMC perspective.

**Additional Items:** None

Ramesh Sood, Ph.D.  
Branch Chief/DPA1/Branch 1/ONDQA

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/s/  
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RAMESH K SOOD  
08/11/2009

**NDA 22-328**

**Zolpidem Tartrate Sublingual Tablet**

**Transcept Pharmaceuticals, Inc.**

**Wendy I. Wilson, Ph. D.**  
**Office of New Drug Quality Assessment**  
**for**  
**Office of Neurology Drug Products**

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## Chemistry Review Data Sheet

1. NDA: 22-328
2. REVIEW: # 01
3. REVIEW DATE: 23-JUL-2009
4. REVIEWER: Wendy I. Wilson, Ph.D.
5. PREVIOUS DOCUMENTS: None.
6. SUBMISSION(S) BEING REVIEWED:

	<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission		30-SEP-2008
Amendment		24-DEC-2008
Amendment		06-FEB-2009
Amendment		12-MAR-2009
Amendment		17-MAR-2009
Amendment		19-MAR-2009
Amendment		22-MAY-2009
Amendment		04-JUN-2009
Amendment		10-JUN-2009
Amendment		10-JUL-2009
Amendment		23-JUL-2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Transcept Pharmaceuticals, Inc.
Address:	1003 W. Cutting Blvd. Pt. Richmond, CA 94804
Representative:	Sharon Sakai, Ph.D., RAC Sr. Director, Reg. Affairs
Telephone:	510-215-3500

8. DRUG PRODUCT NAME/CODE/TYPE:

- |   |                        |
|---|------------------------|
| a) Proprietary Name:                            | Intermezzo® (proposed) |
| b) Non-Proprietary Name (USAN):                 | Zolpidem Tartrate      |
| c) Code Name/# (ONDQA only):                    |                        |
| d) Chem. Type/Submission Priority (ONDQA only): |                        |
| ● Chem. Type:                                   | 3                      |
| ● Submission Priority:                          | S                      |

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(2)
10. PHARMACOL. CATEGORY: Insomnia following middle-of-the-night waking
11. DOSAGE FORM: Tablet
12. STRENGTH/POTENCY: 1.75 mg, 3.5 mg
13. ROUTE OF ADMINISTRATION: Sublingual
14. Rx/OTC DISPENSED:  Rx  OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

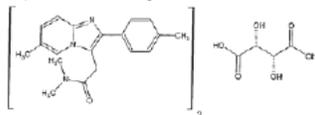
SPOTS product – Form Completed  
 Not a SPOTS product

## Chemistry Review Data Sheet

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: N,N-6-trimethyl-2-p-tolylimidazo[1,2- $\alpha$ ]pyridine-3-acetamide L-(+)-tartrate (2:1)

Mol. Weight: 764.89

Mol. Formula: C<sub>42</sub>H<sub>48</sub>N<sub>6</sub>O<sub>8</sub>

## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		
	IV			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	II			3	Adequate	25-FEB-2008	ANDA
	IV			3	Adequate	18-MAR-2009	
	IV			3	Adequate	13-MAR-2009	
	IV			1	Adequate	10-FEB-2009	

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

## Chemistry Review Data Sheet

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	69209	Zolpidem tartrate sublingual tablet
NDA	19-908	Ambien®

## 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Studies support efficacy.	19-JUN-2009	T. Massie
EES	Acceptable.	01-JUN-2009	S. Ferguson
Pharm/Tox	Acceptable pending labeling.	23-JUL-2009	M. Banks
Biopharm	Acceptable pending labeling.	23-JUL-2009	J. Parepally
LNC	Dosage form is sublingual tablet.	02-DEC-2008	Y. Mille
Methods Validation	Method validation by FDA not required.	16-MAR-2009	W. Wilson
DMEPA	No objection to Intermezzo® name	05-FEB-2009	L. Holmes
EA	Categorical exclusion	16-MAR-2009	W. Wilson
Microbiology	N/A	N/A	N/A

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## Chemistry Review for NDA 22-328

The Executive Summary**I. Recommendations****A. Recommendation and Conclusion on Approvability**

From a CMC perspective, we recommend approval of both the 1.75 mg and 3.5 mg strengths of Intermezzo® (Zolpidem Tartrate) Sublingual Tablets, pending final labeling. We grant a 24 month expiry to both tablet strengths when packaged in (b) (4) foil/foil blister cards and stored at USP Controlled Room Temperature, protected from moisture.

CMC Comments for Approval Letter

- We grant a 24 month expiry to both tablet strengths when packaged in (b) (4) in foil/foil blister cards and stored at USP Controlled Room Temperature, protected from moisture.

**B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**

We have no CMC recommendations for Phase 4 commitments.

**II. Summary of Chemistry Assessments****A. Description of the Drug Product(s) and Drug Substance(s)**

Zolpidem tartrate, the active moiety of the zolpidem tartrate sublingual lozenge, is a non-benzodiazepine hypnotic agent of the imidazopyridine class of drugs. Zolpidem tartrate is a Schedule IV controlled substance. Zolpidem tartrate has a water solubility of 23 mg/ml and has been shown to have oral bioavailability of 70%. Zolpidem tartrate is a white or almost white, hygroscopic, crystalline powder. The zolpidem tartrate used in the Intermezzo® drug product is (b) (4) and exists as (b) (4).

Zolpidem tartrate sublingual tablets are uncoated, biconvex-shaped, and debossed with ZZ on one side. The reverse side is blank. The manufacturer supplies two strengths of drug product, 1.75 mg, and 3.5 mg. The 1.75 mg strength is yellow and the 3.5 mg strength is beige. For each strength, the sublingual tablet weight is 210 mg. (b) (4)

**B. Description of How the Drug Product is Intended to be Used**

The subject of the New Drug Application (NDA) is the zolpidem tartrate sublingual lozenge, 1.75 mg and 3.5 mg, being developed by Transcept Pharmaceuticals, Inc. (Transcept), for the as needed treatment of insomnia characterized by difficulty returning to sleep after awakening in the middle of the night (MOTN). The zolpidem tartrate sublingual lozenge, 3.5 mg, is the planned dose for adult patients older

## Executive Summary Section

than 18 years, but less than 65 years of age, whereas the 1.75 mg strength is the planned dose for patients older than 65 years and other patients with compromised hepatic function. Transcept selected zolpidem tartrate sublingual lozenge, 3.5 mg, as the therapeutic dose for treatment of insomnia in non-elderly adult patients who wake up in the middle of the night and have difficulty returning to sleep. Transcept is proposing an elderly dose of 1.75 mg for zolpidem tartrate sublingual lozenge. This is also consistent with the Ambien® dosing strategy, in which the initial dose in the elderly is 50% of the nonelderly dose.

**C. Basis for Approvability or Not-Approval Recommendation**

We recommend approval of the 1.75 mg and 3.5 mg strengths of Intermezzo® (Zolpidem Tartrate) Sublingual Tablets. The drug substance and drug product information provided in the submission and subsequent amendments support the approval of this application. The drug substance and drug product regulatory specifications adequately control the identity, purity, strength, and quality of each. The drug substance and drug product stability data demonstrate that both remain stable through the proposed re-test and expiry periods. The drug substance and drug product container closures provide adequate protection. The labeling adequately provides the storage, expiry, ingredient, and how supplied information.

**III. Administrative****A. Reviewer's Signature**

*Wendy I. Wilson*

**B. Endorsement Block**

WWilson: 23-JUL-2009  
MHeimann: 23-JUL-2009  
RSood: 28-JUL-2009

**C. CC Block**

DHenry  
CMichaloski

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22328	ORIG 1	TRANSCEPT PHARMACEUTICA LS INC	ZOLPIDEM TARTRATE LOZENGE

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/s/  
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WENDY I WILSON  
07/30/2009

RAMESH K SOOD  
07/30/2009

Initial Quality Assessment  
Branch I  
Pre-Marketing Assessment Division I

**OND Division:** Division of Neurology Products  
**NDA:** 22-328  
**Applicant:** Trancept Pharmaceuticals  
**Stamp Date:** 30-Sep-2008  
**PDUFA Date:** 30-Jul-2009  
**Trademark:** Intermezzo® is proposed  
**Established Name:** zolpidem tartrate  
**Dosage Form:** Lozenge/Tablet  
**Route of Administration:** Sublingual  
**Indication:** Treatment of insomnia following middle-of-the-night waking  
  
**PAL:** Martha R. Heimann, Ph.D.

	YES	NO
<b>ONDQA Fileability:</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<b>Comments for 74-Day Letter</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

## Summary and Critical Issues:

### Summary

*Note: The sponsor refers to the dosage form as a lozenge in the application; the same term is used in this IQA.* (b) (4)

Zolpidem tartrate tablets, 5 mg and 10 mg, are currently marketed by Sanofi under the tradename Ambien® for treatment of short-term insomnia. A number of approved generic products are available. Sanofi also markets zolpidem tartrate extended-release tablets, 6.25 mg and 12.5 mg, under the tradename Ambien CR™ for treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.

Trancept Pharmaceuticals has developed a low dose sublingual zolpidem tartrate product for treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep. The proposed product is a spearmint flavored lozenge/tablet that contains 1.75 mg or 3.5 mg zolpidem tartrate. (b) (4)

The current NDA is submitted as a 505(b)(2) application that references NDA 19-908 (Ambien Tablets). Prior to submission of the NDA, Trancept sought CMC advice via the pre-IND meeting held on November 16, 2004 (with HFD-170), the CMC End of Phase 2 meeting held on June 19, 2007 and a Type C meeting request (written response provided). Most of the questions that were raised by the sponsor during these discussions were deferred as review issues. One significant issue was identified, however. The proposed commercial formulation includes a non-compensial excipient, (b) (4)

(b) (4)  
 The applicant was advised that this would be considered a novel excipient from a CMC perspective. The firm was also advised to consult the clinical division to determine whether any additional nonclinical studies would be needed.

Drug Substance

Zolpidem tartrate drug substance will be manufactured by (b) (4) under DMF (b) (4). The DMF has been reviewed previously and found adequate. [A. Shin review dated 26-Mar-2008]. The applicant has included the acceptance specification for zolpidem tartrate drug substance in the application. The contract manufacturer (b) (4) will test all incoming drug substance lots. Analytical procedures for most tests are included in the NDA or referenced to USP methods. The European Pharmacopeia (EP) is referenced for three tests, i.e., assay, color of solution, and clarity of solution. The EP methods are not included in the NDA.

Drug Product

The proposed product is the Zolpidem Tartrate Sublingual Lozenge (Tablet), which will be available in 1.75 mg and 3.5 mg strengths. Both tablets strength are round, uncoated, biconvex, lozenges debossed with ZZ on one side and blank on the reverse side. Size, shape and weight of both strengths are the same. The only means of differentiation the two strengths is by color. The 1.75 mg strength is yellow; the 3.5 mg strength is beige. The compositions of the commercial are summarized in the sponsor’s Table 1.

**Table 1: Composition of Zolpidem Tartrate Sublingual Lozenges**

Ingredient	Grade	Function	1.75 mg		3.5 mg	
			mg	% w/w	mg	% w/w
Zolpidem Tartrate	-	Active Substance	1.75	(b) (4)	3.5	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Croscarmellose Sodium						
Sodium Stearyl Fumarate						
Silicon Dioxide						
Natural and Artificial Spearmint Flavor						
Silicon Dioxide Colloidal- (b) (4)						
Iron Oxide Beige						
Sucralose						
Iron Oxide Yellow						
Total Lozenge Weight/Percent	-	-	210.00	(b) (4)	210.00	(b) (4)

The lozenge formulation incorporates a (b) (4) (croscarmellose sodium), (b) (4) (b) (4) buffer system, (b) (4) (natural and artificial spearmint), (b) (4) (sucralose). Other excipients include (b) (4) (mannitol, sorbitol, crospovidone, and silicon dioxide), sodium stearyl fumarate, silicon dioxide, and iron oxide. Other than the proprietary excipient, (b) (4) there are no novel excipients. The proposed commercial formulations were used in one Phase 3 clinical study (ZI-12). Earlier IND formulations were manufactured using sodium carbonate (b) (4). Other differences between the commercial formulations and early IND formulations include choice of (b) (4)

The drug product is manufactured by a contract manufacturer, (b) (4). The manufacturing process involves (b) (4)

The proposed drug product specifications are shown below.

**Table 1: Specifications for Zolpidem Tartrate Sublingual Lozenge, 1.75 mg and 3.5 mg**

Test	Specification	Method
Appearance	<b>1.75 mg:</b> Yellow, round, uncoated, biconvex lozenge, debossed with “zz” on one side. <b>3.5 mg:</b> Beige, round, uncoated, biconvex lozenge, debossed with “zz” on one side.	P14100
Identification (HPLC-RT) <sup>a</sup>	Retention time of the zolpidem peak in the sample is within 5% of the zolpidem peak in the reference standard.	835140
Identification (HPLC-UV) <sup>a</sup>	The UV spectrum of the zolpidem peak in the sample nominally matches the spectrum of the zolpidem peak in the reference standard.	835140
Assay	90.0 – 110.0% of label claim	835140
Content Uniformity <sup>a</sup>	Meets USP <905> requirements	835140
Related Substances (report results) Each Unspecified Related Substance Total Related Substances	NMT (b) (4) NMT (b) (4)	835140
pH	9.0 – 10.2	835310
	(b) (4)	855400
Dissolution	Q = (b) (4) at 30 minutes	840920
Disintegration (report results)	NMT (b) (4)	P02920
Microbial Limits <sup>a</sup> Total Aerobic Count Total Yeast & Mold Count <i>Escherichia coli</i> <i>Salmonella species</i> <i>Staphylococcus aureus</i> <i>Pseudomonas aeruginosa</i>	NMT 1000 cfu/g NMT 100 cfu/g Absence Absence Absence Absence	B842400

cfu = colony-forming unit; HPLC = high performance liquid chromatography; NMT = not more than; RT = retention time; UV = ultraviolet.

<sup>a</sup> Required only at release.

The proposed regulatory methods are relatively straight-forward. A single reverse-phase HPLC method is used for assay, related substances, identification and content uniformity. A second reverse-phase method is used for quantitation of dissolution results.

The drug product will be packaged in

(b) (4)

The NDA submission provides 6 months accelerated stability data and 9 months of long-term stability for 6 pilot scale batches (3 per strength) of the commercial formulation.

(b) (4)

[Written communication dated 07-Jul-2007]. The requested comparative moisture permeation data are provided for review.

### ***Critical issues for review***

No critical issues were identified during the initial assessment of the application. Some minor deficiencies were identified (e.g., absence of EP analytical procedures, no stability protocol for post-approval batches). The missing EP procedures are assay (by potentiometric titration) and general tests for appearance of solution. As the drug substance manufacturer's DMF is also referenced for the release specification and associated analytical procedures, absence of the EP procedures from the NDA should be considered a minor deficiency. The deficiencies are readily addressable and should be communicated in the 74-Day Letter.

### ***Additional issues***

*Administrative:* A claim for categorical exclusion under 21 CFR § 25.31(b) is provided in Module 1.

*Establishment Evaluation:* A list of facilities involved in the manufacture, packaging and testing of the drug substance and drug product is appended to this initial assessment. [Attachment 1] All facilities were entered into EES on 23-Oct-2008.

*Labeling/Established Name:* The labeled potency is based the salt form, zolpidem tartrate, not the free base. This is consistent with labeling for the reference drug, Ambien Tablets. Thus, the

salt form should be retained in the established name.

(b) (4)

(b) (4)

(b) (4)

### **Comments for 74-Day Letter**

- 1) The acceptance specification for zolpidem tartrate drug substance references European Pharmacopeia (EP) procedures for assay, color of solution, and clarity of solution. Copies of the EP analytical procedures should be submitted to the NDA.
- 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. The stability commitment should be revised to include the stability protocol for the post-approval commercial batches.

### **Comments and Recommendation:**

The NDA is considered fileable with minor deficiencies to be communicated in the 74-Day Letter. Additional deficiencies may be identified during an in-depth review. The drug substance is not a new molecular entity and the proposed SL formulation is not a novel dosage form. Review by the manufacturing sciences branch does not appear to be needed and assignment of the NDA to a single reviewer is recommended.

Martha R. Heimann, Ph.D.  
Pharmaceutical Assessment Lead

\_\_\_\_\_  
Date

Ramesh Sood, Ph.D.  
Branch Chief

\_\_\_\_\_  
Date

**ATTACHMENT 1**

(b) (4)



IND 69,209

January 24, 2007

Dear Dr. Sakai:

Re: Tradename Review

We have received the Division of Medication Errors and Technical Support (DMETS) consult result on your tradename proposal.

DMETS has no objections to the use of the proprietary name, Intermezzo. This is considered a tentative decision and you should be notified that this name with its associated labels and labeling must be re-evaluated upon submission of the NDA and approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.

DMETS recommends that labels and labeling be submitted for review and comment upon submission of the NDA.

The DDMAC finds the proprietary name Intermezzo acceptable from a promotional perspective.

**Designation of the established name:**

DMETS notes that you characterized the established name and dosage form in different ways in the submission (e.g., “lozenge” and “sublingual (b) (4) zolpidem tartrate”). Therefore, we contacted the Office of New Drugs Quality Assessment (ONDQA) via email for their input on the proper designation of the established name. We received the following response on December 19, 2006:

(b) (4)

(b) (4)

Any questions, please contact me.

Thank you,  
Cathleen

*Cathleen Michaloski, BSN, MPH  
Regulatory Project Manager  
Division of Neurology Products  
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