CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022328Orig1s000

PHARMACOLOGY REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: 7/13/11

FROM: Melissa K. Banks, Ph.D.
Pharmacology / Toxicology Reviewer, HFD-120

SUBJECT: Intermezzo® (zolpidem tartrate sublingual tablets),
NDA #22-328, SDN 34 (1/14/11)

TO: File

This submission is a Class 2 Resubmission for NDA 22-328. The submission contains no new Pharmacology/Toxicology information. Due to clinical deficiencies, the Division is issuing a Complete Response (CR) letter, and labeling will not be addressed in this review cycle.

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/s/

MELISSA K BANKS
07/14/2011

LOIS M FREED
07/15/2011

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application Number:	NDA 22-328
Submission Number/code:	N000
CDER Stamp Date:	Original: September 30, 2008 Also 003 dated 1/12/09, 005 dated 3/5/09, 008 dated 3/17/09 and 009 dated 3/19/09
PDUFA Date:	July 30, 2009; Extended 10/30/09
Product:	Intermezzo® (zolpidem tartrate sublingual tablet)
Indication:	Treatment of Insomnia (characterized by difficulty returning to sleep after awakening in the middle-of-the-night, "MOTN")
Applicant:	Transcept Pharmaceuticals, Inc.
Review Division:	HFD-120; Division of Neurology Products
Reviewer:	Melissa K. Banks, Ph.D.
Supervisor/Team Leader:	Lois M. Freed, Ph.D.
Division Director:	Russell G. Katz, M.D.
Project Manager:	Cathleen Michaloski, BSN, MPH

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1. Executive Summary

1.1. Recommendations

1.1.1. Approvability

This 505(b)(2) application is approvable from a Pharm/Tox perspective.

1.1.2. Additional nonclinical comments

Although the submitted nonclinical local toxicity assay (the only nonclinical study requested) was only marginally adequate, a repeat study would not be likely to provide a great deal of additional useful data and does not appear warranted. The sponsor's submitted study complied with the majority of the design elements outlined by the Agency (see advice letter dated 11/3/06). The nonclinical local toxicity assay, as conducted, demonstrated some potential for mild irritation and potential to aggravate pre-existing tissue injury. The local irritation demonstrated showed evidence of reversibility. Discussion with Dr. Davis (via email, dated 05/05/09) verified that clinically significant oral irritation was not reported in humans.

1.1.3. Labeling

[Note: These recommendations reflect the reviewer's opinion, but have not been subject to internal discussion or external negotiation and may not reflect final labeling.]

(b) (4)

[redacted]

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1.2. Evaluation and discussion of nonclinical findings affecting regulatory decision

1.2.1. Basis of Recommendation

Intermezzo® is a new sublingual oral formulation of approved product, Ambien® (N19-908, zolpidem tartrate). Intermezzo's excipients are compendial (USP), used in approved products (FDA's Inactive Ingredients Guide), or not believed to be of toxicological concern. As the product is believed to be absorbed across the oral mucosae, a nonclinical local toxicity study was required. The sponsor had previously submitted an irritation assay evaluated as inadequate, and received study design advice from the Agency (see advice letter dated 11/3/06, in response to the sponsor's submission of a draft protocol [Serial #022, dated 7/27/06]). The submitted local toxicity study had some notable deficiencies (see P/T review for SDN70, dated 6/29/09), but nonetheless demonstrated some potential for local irritation and aggravation of pre-existing injury to the oral mucosae. The irritation generally showed evidence of reversibility. In this reviewer's opinion, a repeat study of similar duration would not be likely to alter the general conclusion. Additionally, pharmacokinetic/ADME data from humans (e.g., T_{max} and demonstration of a food effect) would appear to indicate that the extent of any transmucosal absorption is not substantial. Clinically significant oral irritation was not reported in the clinical trials, according to the clinical reviewer (Dr. Davis, via email communication dated 05/05/09).

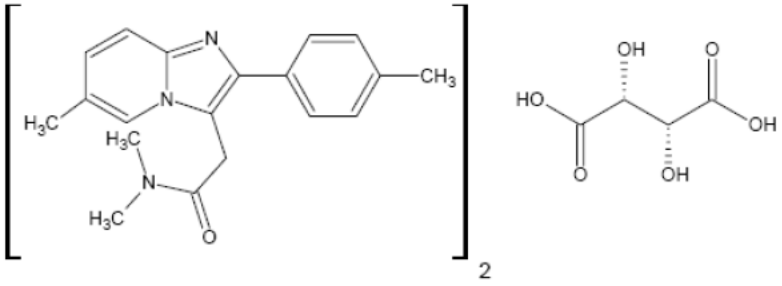
1.2.2. Clinical Implication

n/a

2. Drug Information

2.1. Drug:

2.1.1. Pharmacological class	Sedative/hypnotic, imidazopyridine class, Non-benzodiazepine $GABA_A$ receptor modulator
2.1.2. CAS registry number:	99294-93-6
2.1.3. Generic name:	zolpidem tartrate, zolpidem hemitartrate
2.1.4. Chemical name	bis[*N*,*N*-dimethyl-2-[6-methyl-2-(-4-methylphenyl) imidazo[1,2-*a*]pyridin-3-yl] acetamide](2*R*,3*R*)-2,3-dihydroxybutanedioate OR N,N,6-trimethyl-2-p-tolyl-imidazo[1,2-a] pyridine-3-acetamide L-(+)-tartrate (2:1)
2.1.5. Molecular formula/molecular weight:	$C_{42}H_{48}N_6O_8$; 765
2.1.6. Structure:	[from sponsor's submission]



2.2 Clinical formulation:

2.2.1. Drug formulation:

The Intermezzo® zolpidem sublingual tablet is formulated in strengths of 1.75 mg and 3.5 mg of zolpidem tartrate (see the sponsor's composition table, next page).

(b) (4)

Table 1: Composition of Zolpidem Tartrate Sublingual Lozenge, 1.75 mg and 3.5 mg

Ingredient	Grade	Function	1.75 mg Sublingual Lozenge		3.5 mg Sublingual Lozenge	
			mg	% w/w	mg	% w/w
Zolpidem Tartrate	In-house	Active Substance	1.75	(b) (4)	3.5	(b) (4)
(b) (4)	Supplier's Grade	(b) (4)				
	Supplier's Grade					
Croscarmellose Sodium	USP/NF					
Sodium Stearyl Fumarate	USP/NF					
Silicon Dioxide	USP/NF					
Natural and Artificial Spearmint Flavor	Supplier's Grade					
Silicon Dioxide Colloidal (b) (4)	USP/NF					
Iron oxide Beige	Supplier's grade					
Sucralose	USP/NF					
Iron Oxide Yellow	USP/NF					
Total	-	-	210.00	(b) (4)	210.00	(b) (4)

The zolpidem tartrate sublingual tablet uses Bimucoral™ technology, which is designed to (b) (4) Consequently, it is believed that a portion of each dose is absorbed through the mucosa of the sublingual cavity, while the remainder of the dose is swallowed and absorbed in the gastrointestinal tract.

2.2.2. **Comments on excipients:**

The compendial excipients (croscarmellose sodium, iron oxide yellow, sucralose, silicon dioxide colloidal, silicon dioxide, and sodium stearyl fumarate) used in the zolpidem tartrate sublingual tablet meet the USP compendial specifications. The other excipients (b) (4) iron oxide beige, and natural and artificial spearmint flavor) meet each supplier's specifications. (b) (4) is listed in approved products in the FDA's Inactive Ingredients Guide (IIG); although the amount of (b) (4) is slightly greater than

that listed in the IIG, the calculated amounts of the individual components would be less than those present in a product using similarly comprised (b) (4) (b) (4) with one exception. The only component of (b) (4) not present in (b) (4) Iron oxide beige is a newer (b) (4) Spearmint flavor is also listed in the IIG. Discussion with the CMC Reviewer (Dr. Wilson) indicated that iron oxide is a commonly used dye, although not listed in the IIG. The sponsor previously obtained agreement with the Agency (see minutes dated 5/1/08 and review dated 6/29/09) that further characterization of the (b) (4) both listed in the IIG) would not be needed.

2.2.3. **Comments on impurities/degradants:**
No impurities/degradation products at levels greater than the ICH Q3B (R2) Impurities in New Drug Products (June 2006) identification threshold of (b) (4) have been detected in the zolpidem tartrate sublingual tablets at lot release or during stability studies.

2.3 Proposed clinical population and dosing regimen:

[Taken from the sponsor's draft label, Dosage and Administration]

- Adult dose: 3.5 mg once daily as needed when a middle-of-the-night awakening is followed by difficulty returning to sleep.
- Elderly/debilitated: 1.75 mg once daily as needed when a middle-of-the-night awakening is followed by difficulty returning to sleep.
- Hepatically impaired patients: initial dose 1.75 mg, not to exceed 3.5 mg daily.
- Intermezzo® is supplied as a sublingual tablet. The patient should be instructed to place the tablet under the tongue and allow the tablet to dissolve (b) (4) The tablet should not be chewed or swallowed, and the patient should be instructed to avoid swallowing until the tablet has dissolved. (b) (4) Intermezzo® should not be administered with or immediately after a meal.

2.4Regulatory background:

Previous clinical experience:
The clinical data package contained a total of 12 studies. Clinical safety and efficacy of the zolpidem tartrate sublingual tablet was supported by 2 controlled trials. The NDA also includes studies specifically requested by the Agency to address food effect, relative bioavailability (versus the RLD, Ambien®), and a determination the pharmacodynamic (PD) effects of immediate swallowing of the tablet.

Relevant INDs, NDAs, and DMFs:
RLD: Ambien®, zolpidem tartrate tablets, NDA 19-908

Interactions w/ Agency

The sponsor provided documentation of the following interactions with the Agency (although a CMC meeting held 6/19/07 appears to have been omitted):

- Pre-IND meeting with the Division of Anesthetic, Critical Care, and Addiction Drug Products on12/22/04, minutes dated 1/21/05
- Original IND 69,209 submitted to the Division of Neurology Products on 4/15/05
- Type C clinical meeting to discuss clinical development plans for supporting a claim of middle-of-the-night insomnia on 1/10/06, minutes dated 2/9/06
- Type B End-of-Phase 2 clinical meeting to gain final agreement on the clinical development program on 1/17/07, minutes dated 2/6/07
- Pre-NDA meeting on 4/2/08, minutes dated 5/1/08.

3. Studies submitted within this submission:

3.1. Studies reviewed within this submission:

n/a

3.2. Studies <u>not</u> reviewed within this submission:

n/a

3.3. Previous reviews referenced:

See P/T review dated 6/29/09, for review of the nonclinical local toxicity assay.

Notes: SD= single dose, LD= low dose, MD= medium dose, HD= high dose, M= male, F= female, D= day, Wk= week, Mo= month; [ss]= statistically significant, [nss]=not statistically significant, gp=group, conc=concentration; trtmt=treatment; RLD= reference-listed drug

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

5. PK/ADME/TK

Intermezzo® contains the same active ingredient (zolpidem tartrate) as Ambien®, but at a 65% lower dose. The overall relative bioavailability of the 3.5 mg Intermezzo sublingual tablet was approximately 38% of that of the 10 mg oral zolpidem tartrate tablet (Ambien®). The pharmacokinetics of the zolpidem tartrate sublingual tablet was characterized by rapid absorption and an elimination half-life in the same range as the elimination half-life of Ambien® (2.2 to 2.5 hrs). The plasma concentration 15 minutes after dosing was greater for the 3.5 mg zolpidem tartrate sublingual tablet than for 10 mg Ambien®. Like Ambien®, the overall bioavailability of the zolpidem tartrate sublingual tablet is reduced by food; however, the first 15-minute fasted and fed plasma concentrations overlapped in the study (suggesting a reduced food effect for the portion of the zolpidem tartrate sublingual tablet presumed absorbed through the oral mucosae). See sponsor's summary table 2 for comparisons.

Table 2: Comparison of PK Parameters for the Zolpidem Tartrate Sublingual Lozenge for Proposed Doses in Elderly and Non-Elderly Subjects vs. the Reference Listed Drug (Ambien® 10 mg)

Parameter (Units)	Elderly Adults (1.75 mg dose)	Nonelderly Adults (3.5 mg dose)	Oral Zolpidem (Ambien® 10 mg)
C_{max} (ng/mL)	40.66	57.18	146.60
$C_{15\ min}$ (ng/mL)	30.30	19.85	12.49
$C_{20\ min}$ (ng/mL)	33.49	30.48	36.11
$C_{4\ hr}$ (ng/mL)	17.55	26.69	76.84
$AUC_{0\text{-}8h}$ (ng·h/mL)	164.90	201.40	525.29
$AUC_{0\text{-}15\ min}$ (ng·h/mL)	NR	1.93	0.64
$AUC_{0\text{-}20\ min}$ (ng·h/mL)	NR	4.00	2.68
$AUC_{0\text{-}1h}$	NR	32.59	67.32
$AUC_{0\text{-}Tmax}$	NR	41.61	73.26
$AUC_{0\text{-}4\ hr}$ (ng·h/mL)	100.50	145.48	362.85
$t_{1/2el}$ (hr)	2.75	2.23	2.33
Mean T_{max} (hr)	0.62	1.21	1.18

$AUC_{0\text{-}t}$=area under the concentration-time curve from time zero to time of last non-zero; $AUC_{0\text{-}15\ min}$=area under the concentration-time curve from time zero to 20 minutes postdose; $AUC_{0\text{-}20min}$=area under the concentration-time curve from time zero to 20 minutes postdose; $AUC_{0\text{-}4\ hr}$=area under the concentration-time curve from time zero to 4 hours postdose; C_{max}=maximum observed plasma concentration, $C_{15\ min}$=observed concentration at 15 minutes postdose; $C_{20\ min}$=observed concentration at 20 minutes postdose; $C_{4\ hr}$=observed concentration at 4 hours postdose; NR=not reported; $t_{1/2el}$=elimination half-life; T_{max}=time of maximum observed plasma concentration.

Source: Section 5.3.3.1.2, Table 16, Table 25 (elderly); Section 5.3.3.1.3, Table 15, Table 24, Table 26 (nonelderly).

10. Special toxicology studies:

Only a nonclinical local toxicity assay was requested and conducted (see P/T review dated 6/29/09), since Intermezzo® is believed to be partially absorbed across the oral mucosae. The study demonstrated some potential for mild irritation (mostly at 2 times the clinical dosing frequency), as well as potential to aggravate pre-existing tissue injury and impair wound healing (as demonstrated in abraded mucosae). The local irritation demonstrated showed evidence of reversibility.

11. Overall integrated summary and safety evaluation:

This is a 505(b)(2) application, relying on the findings of safety for Ambien®(NDA 19-908). Other than a local toxicity study, no additional nonclinical studies were conducted for the NDA application. With regard to the nonclinical data cited for Ambien® upon which the sponsor relies, the difference in the MRHD dose (3.5 mg zolpidem tartrate in Intermezzo® versus 10 mg zolpidem tartrate in Ambien®) will be addressed by modifying the relevant safety margins in labeling; relative exposures were roughly proportional to dose. These margins will be based on body-surface-area dose comparisons (in mg/m^2).

Consideration is being given to requesting studies in pediatric patients for Intermezzo®, as a Phase 4 commitment. If the clinical team determines that a pediatric study will be necessary due to the change in route, altered MRHD and administration details, a juvenile animal toxicology study(ies) will likely be required to support the clinical trial(s).

12. Appendix/Attachments

n/a

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/s/

Melissa Banks
7/22/2009 08:17:04 PM
PHARMACOLOGIST

Lois Freed
7/23/2009 06:51:37 AM
PHARMACOLOGIST
I concur, with minor revisions to recommended labeling.