CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022328Orig1s000

SUMMARY REVIEW

MEMORANDUM

DATE: November 23, 2011

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 22328

SUBJECT: Action Memo for NDA 22328, for the use of Intermezzo (zolpidem tartrate sublingual) 1.75 mg and 3.5 mg to treat insomnia following middle of the night (MOTN) awakening

NDA 22328, for the use of Intermezzo (zolpidem tartrate sublingual) 1.75 mg and 3.5 mg to treat insomnia following middle of the night (MOTN) awakening, was submitted by Transcept Pharmaceuticals, Inc., on 9/30/08. Intermezzo is to be taken once during the night, as needed, if a patient wakes up and cannot readily fall back to sleep. The sponsor had proposed that patients take the drug at night only if they had at least 4 hours of sleep remaining.

The division issued a Complete Response (CR) letter to the sponsor on 10/28/09, citing several reasons for the action, related to questions about the safe use of the product. Specifically, the division was concerned that some patients would have zolpidem levels at 4 hours (or more) after dosing that would produce significant impairment, including possible deleterious effects on driving. Further, the division expressed concern that patients might take more than one dose/night, and that some patients would take the drug with fewer than 4 hours of sleep remaining, all maneuvers that would result in even higher zolpidem levels in the morning.

The division had concluded that effectiveness had been established.

The sponsor responded to the CR letter with a submission dated 1/14/11. In that submission, the sponsor, among other things, submitted the results of a driving study, in which patients' driving performance was assessed at 3 and 4 hours after receiving a 3.5 mg dose.

After review of that submission, the division had several residual concerns.

Specifically, the division concluded that an unacceptable number of patients had unacceptably high zolpidem levels 4 hours post dosing, levels that would be expected to adversely affect driving. In the driving study, there was clear impairment at 3 hours post-dosing, and there was evidence (from other sources), that a non-trivial subset of patients would have zolpidem levels at 4 hours that approximated the average plasma levels at 3 hours, a time, again, at which driving was clearly impaired.

Further, we remained concerned that some patients would take the drug with less than 4 hours of sleep remaining. We did, however, conclude that the sponsor adequately minimized the likelihood that patients would take more than one dose/night (based on proposed labeling and revised packaging).

Because of these remaining safety concerns, the division issued a second CR letter on 7/14/11. In this letter, we asked the sponsor to further characterize the distribution of zolpidem plasma levels achieved in the morning after dosing, and that the sponsor explore strategies to decrease morning plasma levels (for example, through revised dosing recommendations, patient selection, etc.).

After the issuance of the second CR letter, members of the review team and Dr. Robert Temple, Director, Office of Drug Evaluation (ODE) I, and Dr. Ellis Unger, Deputy Director, ODE I, met with the sponsor on 9/14/11. At that meeting, the sponsor proposed that, in order to address the division's concerns, they revise their proposed dosing instructions to recommend a dose of 1.75 mg in women and 3.5 mg in men, based on the finding that plasma levels in women are about 40-70% greater than those in men; this finding is essentially independent of weight. They further proposed recommending (b) (4) (b) (4) At the meeting, the division agreed to entertain this approach, and the sponsor submitted their response to the second CR letter on 9/27/11.

This submission has been reviewed by Dr. Christopher Breder, medical officer; Dr. Julie Villanueva, Division of Medication Error Prevention and Analysis; Dr. Meeta Patel and Dr. Quynh-Van Tran, Office of Prescription Drug Promotion; Robin Duer, Division of Risk Management; Dr. Lyudmila Soldatova, Office of New Drug Quality Assessment; Dr. Jagan Parepally, Office of Clinical Pharmacology; Dr. Stephen Sun, Controlled Substance Staff; and Dr. Ronald Farkas, neurology team leader and Cross Discipline Team Leader.

The review team recommends that the application be approved.

In particular, the team is convinced by the sponsor's re-analyses and presentation of the pharmacokinetic data that the average plasma level in women 4 hours after a dose of 1.75 mg (about 16 ng/mL) is in the range of the average zolpidem plasma level in men (about 21 ng/mL) 4 hours after a 3.5 mg dose. Further, and critically, the sponsor has calculated the following probabilities of various zolpidem plasma levels in women at the following times after a 1.75 mg dose, and analogous probabilities in men after a 3.5 mg dose:

Predictive Probabilities of Zolpidem Plasma Levels

Women

Concentrations	3 hours	4 hours	5 hours
20 ng/mL	0.5	0.3	0.14
30 ng/mL	0.1	0.03	0.006
40 ng/mL	0.01	0.001	0.000
>40 ng/mL	0	0	0

Men

Concentrations	3 hours	4 hours	5 hours
20 ng/mL	0.7	0.5	0.26
30 ng/mL	0.35	0.14	0.03
40 ng/mL	0.085	0.014	0.001
50 ng/mL	0.01	0.001	0
60 ng/mL	0.001	0	0

Effectiveness

The sponsor re-analyzed study ZI-06-010, which was a single dose, placebo controlled, cross-over study in which Intermezzo 1.75 mg, 3.5 mg, and placebo were given to 58 women and 24 men. The primary outcome was latency to persistent sleep (LPS) after a scheduled MOTN awakening, as assessed by polysomnography (PSG). The results for women given a 1.75 mg dose and men given a 3.5 mg dose on the primary (LPS) and other outcomes (sleep onset latency [SLO]; total sleep time [TST]; and subjective TST [sTST]) are given below (as described by Dr. Breder, the results are presented as change from baseline, least square means):

Outcome	Women			Men		
	ZPM	Pbo	P-value	ZPM	Pbo	P-value
LPS (min)	15.7	27.7	<0.0001	12.7	29.0	<0.0001
SOL (min)	28.4	38.5	0.0008	21.9	38	0.0001
TST (min)	199.5	185.2	0.003	207	178.3	<0.0001
sTST (min)	161.4	148	0.03	169.3	146.8	0.04

Dr. Breder also performed an analysis of the effectiveness of a dose of 1.75 mg in men; if this dose is effective in men (who would clearly have lower plasma levels than women receiving a dose of 1.75 mg) this would lend further support to

the effectiveness of a 1.75 mg dose in women, given that there would otherwise be no “replication” of the effectiveness of this dose, and given that men who receive a 1.75 mg dose of zolpidem will have lower plasma levels than women given that same dose. As he reports, the p-value for the 1.75 mg-placebo contrast in men on LPS was 0.03.

Comments

As described by both Drs. Breder and Farkas, the sponsor’s most recent submission establishes that the plasma levels achieved 4 hours post-dosing in women who receive a 1.75 mg dose and in men who receive a 3.5 mg dose of Intermezzo are consistently and reliably in a range considered to be associated with an acceptably minimal risk of driving impairment (<40 ng/mL). Even if patients take a dose with only 3 hours of sleep remaining, the number of patients, at these dosing recommendations, who would have plasma levels in a range considered to be problematic would be small. Further, the sponsor has demonstrated the effectiveness of a 1.75 mg dose in women. Even though the study in which this dose was examined was a single dose study, it included both objective and subjective measures, and the fact that the plasma levels in women at 1.75 mg are in the range of those produced by a 3.5 mg dose in men (for whom there is longer term effectiveness data), establishes the utility of the 1.75 mg dose in the longer term.

For these reasons, I agree with Drs. Breder and Farkas that this application can be approved.

There are, however, several studies that the sponsor must perform as post-marketing requirements (PMRs).

First, because we are still concerned that patients may administer the drug inappropriately (e.g., with less than 4 hours of sleep remaining), we will require the sponsor to perform an actual use study, including a comparative hypnotic.

Finally, we will require the sponsor to study Intermezzo in pediatric patients 6 years old and older with MOTN in the setting of ADHD. This program will include a pharmacokinetic/tolerability study, a controlled effectiveness trial, and a long-term safety study.

For the reasons given above, then, I will issue the attached Approval letter, with the attached agreed upon labeling, Medication Guide, and Instructions for Use.

Russell Katz, M.D.

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

/s/

RUSSELL G KATZ
11/23/2011

Cross-Discipline Team Leader Review

Date	11/18/2011
From	Ronald Farkas MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA 22328 Complete Response
Applicant	Transcept Pharmaceuticals
Date of Submission	September 27, 2011
PDUFA Goal Date	11/27/2011
Proprietary Name / **Established (USAN) names**	Intermezzo zolpidem tartrate
Dosage forms / Strength	1.75 mg / 3.5 mg tablets
Proposed Indication(s)	Insomnia following middle-of-the-night awakening
Recommended:	Approval

1. Introduction

The original NDA application for Intermezzo received a Complete Response Letter on October 28, 2009. The Division agreed that efficacy for insomnia following middle-of-the-night (MOTN) awakening was adequately supported, but was concerned about the safety risk from residual morning levels of drug, particularly if there was inadvertent re-dosing of Intermezzo in a single night, or inadvertent dosing with less than 4 hours of bedtime remaining. The Division indicated in the CR letter that it appeared necessary for the sponsor to demonstrate the following:

1. That Intermezzo, when taken as directed, does not unacceptably impair driving ability.
2. That dosing errors can be adequately minimized, or that the potential adverse effects of such dosing errors on driving safety can be shown to be acceptable.

The sponsor submitted a Complete Response on January 14, 2011, to which the Division issued a second Complete Response on 7/14/2011. The Division agreed that the sponsor had adequately mitigated the risk of inadvertent re-dosing of Intermezzo through the proposed individual-dose packaging and associated patient instructions. The Division additionally concluded that while it would not compel the sponsor to conduct additional studies addressing the risk of dosing with less than 4 hours of bedtime remaining, the safety review of Intermezzo would have to take into consideration that some late dosing would inevitably occur in clinical practice.

During review of the Complete Response, the Division became concerned that patients at the high end of zolpidem exposure from Intermezzo would be at unacceptable risk of next-day impairment. Women, in particular, had on average 40-

to 70% higher zolpidem plasma levels at a given dose than men. The Division indicated in the CR letter that it appeared necessary for the sponsor to demonstrate the following:

1. Characterize more thoroughly the distribution of blood levels that can occur the morning after Intermezzo dosing.
2. Pursue strategies to decrease morning zolpidem levels from Intermezzo, particularly levels at the high end of the distribution (e.g. through modification of dose, time, patient selection, etc.).
3. Depending on the residual zolpidem level that might result after mitigation strategies were implemented, demonstrate that the levels did not present an unacceptable risk of next-day impairment.

The Division met with the Sponsor at an End of Review meeting on September 14, 2011. The sponsor proposed addressing the Division's safety concerns by decreasing the recommended dose in women to 1.75 mg, (b) (4) The Division generally agreed with the sponsor's proposal, and that a Complete Response based on their arguments could be considered a Class 1 Resubmission.

Dr. Christopher Breder was the primary clinical reviewer for this submission. Dr. Jagan Parepally was the primary reviewer from the Office of Clinical Pharmacology.

2. Complete Response

The Sponsor's Complete Response presented efficacy, pharmacokinetic, and safety data supporting the proposed dose recommendations for Intermezzo.

a. Pharmacokinetic data concerning next-morning zolpidem levels

Average zolpidem level

The sponsor finds that pooled data from Intermezzo pharmacokinetic studies suggests that the average 4-hour post-dose plasma level of zolpidem in women following the 1.75 mg dose (about 16 ng/ml) is in a similar range to the 4-hour levels in men following the 3.5 mg dose (about 21 ng/ml).

Probability of zolpidem level ≥ 40 ng/ml

The tables below shows the sponsor's calculation of the probability of a subject being exposed to a plasma zolpidem level of ≥ 40 ng/ml at 3, 4, and 5 hours post dose.

Women: probability of zolpidem level ≥ 40 ng/ml

Plasma concentrations (ng/ml)	Predictive probabilities Intermezzo 1.75 mg[a]		
	3 hour	4 hour	5 hour
10	0.875	0.810	0.646
20	0.492	0.304	0.138
30	0.116	0.030	0.006
40	0.010	0.001	0.000
50	0.000	0.000	0.000
60	0	0	0

Men: probability of zolpidem level ≥ 40 ng/ml

Plasma concentrations (ng/ml)	Predictive probabilities Intermezzo 3.5 mg[a]		
	3 hour	4 hour	5 hour
10	0.946	0.891	0.741
20	0.733	0.529	0.263
30	0.351	0.137	0.029
40	0.085	0.014	0.001
50	0.010	0.001	0.000
60	0.001	0.000	0.000

b. Effect of other demographic factors on Intermezzo plasma levels

The sponsor analyzed zolpidem plasma level across PK studies by age (non-elderly-age), body weight, and race (African American and non-African American), concluding that these factors did not significantly influence Intermezzo levels. The sponsor did conclude, however, that there was somewhat greater variability in African-American men (see table below).

RACIAL DISTRIBUTION OF MALE SUBJECTS AMONG
PLASMA CONCENTRATION CATEGORIES AT 3-HOUR, 4-HOUR,
AND 5-HOUR SAMPLING TIMES

Plasma level category (ng/mL)	C3		C4		C5	
	Total	AfAm	Total	AfAm	Total	AfAm
0-10	3	1 (33%)	8	3 (38%)	27	10 (31%)
10-20	22	10 (46%)	41	15 (37%)	46	11 (24%)
20-30	38	10 (26%)	38	12 (32%)	18	10 (56%)
30-40	24	7 (29%)	7	3 (43%)	4	3 (75%)
40-50	7	5 (71%)	2	2 (100%)	1	1 (100%)
50-60	1	1 (100%)	0	—	0	—
Chi-square	8.5 (N.S.)		4.0 (N.S.)		10.3 ($p<0.05$)	

Table 4, briefing-meeting-type-a-20110914.pdf

Dr. Breder concludes that the dose reduction in females mitigates the concern about the impairing effects of residual morning levels of zolpidem. In addition to reviewing the sponsor's tables, Dr. Breder analyzed zolpidem level in study ZI-05-009 by gender, dose, and time after dosing, with findings supportive of the sponsor's analysis.

Dr. Parepally similarly concludes that dose reduction in females mitigates the concern about impairing effects of residual morning levels of zolpidem. Further adjustment of dose by weight is not warranted, as zolpidem clearance was not related to weight. Race (African-Americans and non-African-Americans) did not significantly influence zolpidem plasma levels. In African-American men, greater variability was seen in zolpidem levels compared to non-African-American men; in contrast, in women no difference in variability associated with race was observed.

CDTL Discussion:
The Division was concerned that zolpidem blood levels higher than about 40 ng/ml could be associated with clinically meaningful driving impairment. With the revised dosing of 1.75 mg in women, and 3.5 mg in men, zolpidem blood levels at 4 hours are usually at or below 40 ng/ml, and almost always below 50 ng/ml. I agree with Dr. Breder and Dr. Parepally that zolpidem levels with revised dosing do not pose an unacceptable risk of impairment (see additional discussion under *Section 5, Recommendations/Risk Benefit Assessment*).

Greater variability of zolpidem levels was observed in African-American men compared to non-African-American men, but the difference is unlikely to be clinically meaningful; in particular, the maximum blood level observed at 4 hours post-dosing in African-American men did not exceed 50 ng/ml.

c. Driving Safety

The sponsor argues that the driving study (ZI-18) demonstrated that Intermezzo 3.5 mg significantly affects driving performance at 3 hours, but not at 4. They note, however, that impairment at 3 hours would be less if women had taken the new recommended dose of 1.75 mg.

The sponsor proposes that to provide a greater margin of safety, (b) (4) The sponsor notes that this recommendation seems to be consistent with FDA concern regarding patient misdosing relative to the originally proposed 4-hour interval between dosing and wake-time, and also to offer a next-day checkpoint for patient decisions regarding the time between MOTN dose and driving.

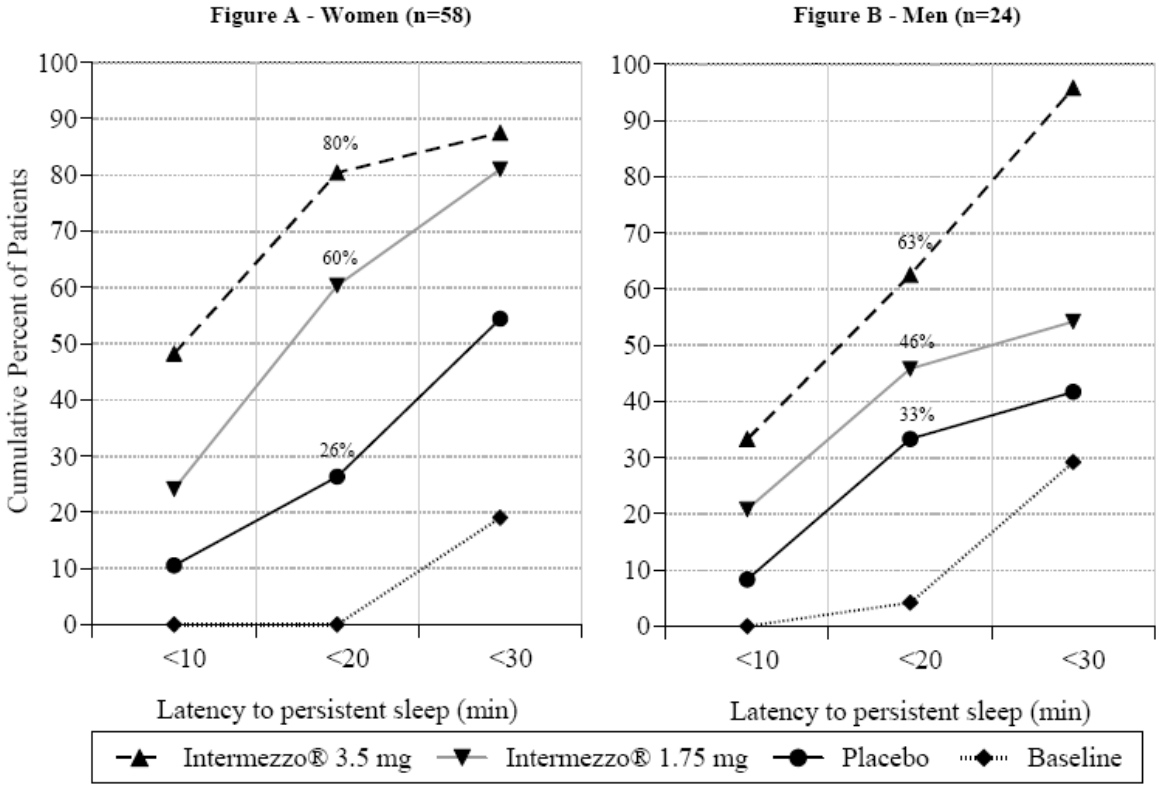
Dr. Breder and Dr. Parepally conclude that zolpidem blood levels are adequately low at 4 hours, (b) (4)

CDTL discussion: (b) (4) **with 1.75 mg as the recommended dose in women. Even in patients who might drive 3, instead of 4 hours after dosing, only about 1% of women would have a zolpidem level of 40 ng/ml, and almost none would have higher levels. In men 3 hours after the 3.5 mg dose, about 10% would have a blood level of 40 ng/ml, but only about 1% would have a blood level of 50 ng/ml.**

d. Efficacy data

The division previously concluded that the 3.5 mg Intermezzo dose was effective in both men and woman. The sponsor cites study ZI-06-010 in support of efficacy of the proposed 1.75 mg Intermezzo dose in women. The study was a double-blind, placebo-controlled crossover study in 82 patients, of which 58 were female and 24 male. Latency to persistent sleep after scheduled middle-of-the-night awakening was the primary endpoint. The 1.75 mg dose was statistically superior to placebo in women. Average efficacy of the 1.75 mg dose in women was roughly similar to efficacy of the 3.5 mg dose in men (figure 1 from sponsor submission, below).

Figure 1: Cumulative % of Patients Asleep (After MOTN Awakening) at Sequential 10-minute Intervals by PSG (Study ZI-06-010)



Dr. Breder conducted an independent analysis of LPS-MOTN in study ZI-06-010, finding statistically significant evidence of efficacy of the 1.75 mg dose in women. His overall conclusion is that the 1.75 mg dose in women has similar efficacy to the 3.5 mg dose in men.

CDTL discussion: I agree that the 1.75 mg dose is both statistically and clinically meaningfully effective in women. The efficacy of the 1.75 mg dose in women is roughly similar to that of the 3.5 mg dose in men.

3. Pediatrics

The Intermezzo pediatric partial waiver, deferral, and plan were reviewed by the PeRC Subcommittee on September 2, 2009. DNP recommended a partial wavier from 0-5 years because the disease/condition does not exist in this age group, and a deferral for studies in children 6- to16 years because the product is ready for approval in adults.

4. Other Relevant Regulatory Issues

- Dr. Lyudmila Soldatova in the Office of New Drug Quality Assessment recommends approval. The Office of Compliance stated that all facilities listed in the original application are current.
- Dr. Stephen Sun in the Controlled Substance Staff did not identify any issues that would preclude approval.
- Patient labeling review was conducted by Robin Duer, who found the medication guide and instructions for use acceptable with DRISK's recommendations.

5. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approval

- Risk Benefit Assessment

Efficacy
In the first review cycle for Intermezzo, the Division concluded that efficacy had been adequately demonstrated. In the inpatient study, both the 1.75 and 3.5 mg doses were effective in adults. In the outpatient study only the 3.5 mg dose was examined, and was found to be effective. To address the Division's concerns about next-day impairment, the Sponsor currently proposes a 1.75 mg dose in women (retaining the 3.5 mg dose in men). While the 1.75 mg dose was examined in only one study, once efficacy was established for Intermezzo, specific dosing recommendations can be based on data not specifically replicated in two studies. I therefore conclude that efficacy has been adequately demonstrated.

Safety
After review of previous submissions, the Division concluded that, aside from concerns about next-day impairment, the safety of Intermezzo had been adequately demonstrated. I conclude from the current submission that the sponsor has adequately addressed concerns about next-day impairment.

FDA, as well as other government agencies and the wider public, has become increasingly concerned about the risk posed by driving while impaired by medications. However, while research efforts and policy discussions on the issue have been increasing, it remains unclear how best to mitigate, or perhaps even to assess the magnitude of this risk. Despite this lack of clarity, it appears necessary for FDA to consider the risk of impaired driving in current new drug approvals while the complex scientific and policy issues involved are addressed on an ongoing basis.

A number of approaches to evaluating and responding to drug-impaired driving have been widely discussed, and appear reasonable to apply to current drug approval. One approach considers the legal definition of alcohol-impaired driving, at least in broad terms, as a relevant benchmark for evaluating the acceptability of risk from drug-impaired driving. Of note, the 0.05% blood alcohol level is often used as a cutoff in driving impairment studies because it is the legal limit for driving in many countries; however, in the United States, the blood alcohol level that is illegal *per se* is 0.08%. The impairment from this higher alcohol level might therefore be a more appropriate benchmark for evaluating the acceptability in the United States of adverse effects of drugs on driving.

While a substantial amount of published work addresses the type and magnitude of driving impairment from alcohol, little attention appears to have been given to collecting data that could be used most effectively for comparison testing. For example, a 2.5 cm change in SDLP is often cited as corresponding to an 0.05% blood alcohol level (and about a 4 cm change as corresponding to 0.08% blood alcohol), but variability in this value appears to be poorly defined. When comparing the effects of a drug to that of alcohol, a certain difference (higher or lower) is likely to be found at least due to random variability alone, but little information is available about how large a difference is clinically or statistically meaningful. Also, fundamentally, the degree to which SDLP truly quantifies driving risk from alcohol or other drugs is incompletely understood. Because of the above concerns, reasonable consideration must be given to limitations in both the accuracy and precision of findings from the Intermezzo driving study.

For Intermezzo, analysis of SDLP by the 'symmetry analysis' showed a statistically significant effect at 3 hours after the 3.5 mg dose, in a study with half men and half women. The symmetry analysis, by design, attempts to identify if there is a greater than expected proportion of patients whose driving deteriorates versus improves after drug. At the 2.5 cm threshold, roughly 25% of the patients experienced impairment (10 were 'impaired', 29 'unchanged', and 1 'improved'; see Appendix). On the premise that, in general, impairment increases with increasing zolpidem blood levels, it thus seems reasonable to conclude that roughly the highest 25th percentile of zolpidem blood levels would, experimental noise and other sources of variability aside, correlate with SDLP impairment. In women, who represent most of those with high zolpidem levels, the upper quartile blood level 3 hours after the 3.5 mg dose is roughly 45 ng/ml.

Results at 4 hours seem to confirm the findings at 3 hours. While the symmetry analysis was not statistically significant at 4 hours, roughly 10% of subjects were nominally impaired (5 'impaired', 34 'neutral', 1 'improved'). At 4 hours, the upper 10th percentile of zolpidem blood levels in women is roughly 45 ng/ml, similar to the estimate for the impairing level at 3 hours.

At larger SDLP thresholds of about 4- to 4.25 cm that correspond roughly to impairment from alcohol at the 0.08% legal level in the United States, results at 3

hours after Intermezzo suggested that about 10- to 15% of subjects were impaired. This would correspond to a zolpidem level of about 55 ng/ml. At 4 hours post-dosing, there was essentially no evidence of impairment at this SDLP level (1 'impaired' 39 'neutral', 0 'improved'). This is consistent with data from PK studies that zolpidem blood levels are usually below 55 ng/ml 4 hours after dosing, even in women.

With the revised dosing recommendation (1.75 mg for women and 3.5 mg for men), blood levels at 4 hours for both men and women are usually below 40 ng/ml, and almost always below 50 ng/ml. Reassuringly, even at 3 hours, almost no women would have blood levels above 40 ng/ml, and only about 1% of men would have blood levels of 50 ng/ml.

Even with the considerable uncertainty in the clinical interpretation of SDLP data, I find the results above to be adequately reassuring of safety. While some measurable level of 'driving impairment' (at least as understood by SDLP) may be present in patients the morning after use of Intermezzo, even in patients at the high end of the blood level distribution, this impairment appears acceptable in the context of the higher degree of impairment from alcohol that is acceptable while driving. Particularly in the context of a drug with benefits as well as risks, the possibility of a small degree of driving impairment seems acceptable.

The Division had also been concerned that with previous dosing recommendations morning blood levels in some patients were substantially above those shown to be effective at decreasing sleep latency after middle-of-the-night awakenings. It seemed likely to the Division that at high enough morning zolpidem levels, there would be an increased risk of falling asleep while driving. In efficacy studies, average Cmax after the 1.75 mg dose is about 30- to 35 ng/ml. This blood level, even with the lower dosing now proposed for women, would still occur in some patients 4 hours after dosing. Importantly, however, the Division's previous concern was not so much that morning blood levels could be near those associated with nighttime efficacy, but rather that in some patients morning blood levels were *several times higher* than those associated with nighttime efficacy. The propensity to sleep is high at night and low in the morning, and a blood level associated with efficacy at night, when patients were trying to fall asleep, would not necessarily cause a clinically meaningful effect on propensity to sleep in the morning, when patients were active and trying to stay awake. I therefore find this concern to have been adequately addressed.

In addition to the dose change, the sponsor proposed in their Compete Response (b) (4) [redacted] On-face this might seemingly increase safety, since even a small residual effect of zolpidem might theoretically increase the risk of traffic accidents. However, there are many potential adverse consequences of highly restrictive and complex labeling of Intermezzo, including shifting patients to use of drugs that have more potential for next-day impairment than Intermezzo, or distracting patients from more important factors affecting safety, such as dosing only once per night. While risk can not be totally excluded at the residual zolpidem levels predicted to occur, I believe that there is adequate reassurance that Intermezzo is

safe if the 4 hour interval is followed, even allowing for some degree of late dosing errors.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

The usual methods of postmarketing surveillance, such as spontaneous adverse events reporting, are unlikely to allow for adequate identification or quantification of adverse events caused by failure to take Intermezzo as labeled. For example, motor vehicle accidents, a key safety concern, occur at such a high background frequency that a clinically meaningful increase in risk attributable to Intermezzo would not readily be detectible with usual surveillance methods. Therefore, the sponsor should conduct a study to determine patient compliance with dosing instructions in the setting of actual clinical use. The study should enroll patients representing the clinical population using the drug, and should assess the incidence, nature, causes, and consequences of departures from dosing instructions. The study should include a comparator group that is taking other drugs approved for insomnia characterized by difficulty with sleep maintenance.

Appendix

Intermezzo 3-hours post-dose

Levels of Threshold in Relation to Impaired Driving Performance and P-values

Treatment Versus Placebo	Number of Subjects				Probability		McNemar Statistic	p-value
	Threshold (cm)	Impaired	Neutral	Improved	Impaired	Improved		
ZST 3h	1.75	16	21	3	0.400	0.075	8.89	0.0044
	2	13	25	2	0.325	0.050	8.07	0.0074
	2.25	11	27	2	0.275	0.050	6.23	0.0225
	2.5	10	29	1	0.250	0.025	7.36	0.0117
	2.75	10	29	1	0.250	0.025	7.36	0.0117
	3	10	30	0	0.250	<.001	10.0	0.0020
	3.25	8	32	0	0.200	<.001	8.00	0.0078
	3.5	7	33	0	0.175	<.001	7.00	0.0156
	3.75	6	34	0	0.150	<.001	6.00	0.0313
	4	6	34	0	0.150	<.001	6.00	0.0313
	4.25	4	36	0	0.100	<.001	4.00	0.1250
	4.5	3	37	0	0.075	<.001	3.00	0.2500
	4.75	3	37	0	0.075	<.001	3.00	0.2500
	5	2	38	0	0.050	<.001	2.00	0.5000
	5.25	2	38	0	0.050	<.001	2.00	0.5000
	5.5	2	38	0	0.050	<.001	2.00	0.5000
	5.75	2	38	0	0.050	<.001	2.00	0.5000
	6	2	38	0	0.050	<.001	2.00	0.5000
	6.25	1	39	0	0.025	<.001	1.00	1.0000
	6.5	1	39	0	0.025	<.001	1.00	1.0000

Intermezzo 4-hours post-dose

Levels of Threshold in Relation to Impaired Driving Performance and P-values

Treatment Versus Placebo	Number of Subjects				Probability		McNemar Statistic	p-value
	Threshold (cm)	Impaired	Neutral	Improved	Impaired	Improved		
ZST 4h	1.75	8	29	3	0.200	0.075	2.27	0.2266
	2	6	33	1	0.150	0.025	3.57	0.1250
	2.25	5	34	1	0.125	0.025	2.67	0.2188
	2.5	5	34	1	0.125	0.025	2.67	0.2188
	2.75	4	36	0	0.100	<.001	4.00	0.1250
	3	3	37	0	0.075	<.001	3.00	0.2500
	3.25	2	38	0	0.050	<.001	2.00	0.5000
	3.5	2	38	0	0.050	<.001	2.00	0.5000
	3.75	2	38	0	0.050	<.001	2.00	0.5000
	4	1	39	0	0.025	<.001	1.00	1.0000
	4.25	1	39	0	0.025	<.001	1.00	1.0000
	4.5	1	39	0	0.025	<.001	1.00	1.0000
	4.75	1	39	0	0.025	<.001	1.00	1.0000
	5	1	39	0	0.025	<.001	1.00	1.0000
	5.25	1	39	0	0.025	<.001	1.00	1.0000
	5.5	1	39	0	0.025	<.001	1.00	1.0000
	5.75	1	39	0	0.025	<.001	1.00	1.0000
	6	1	39	0	0.025	<.001	1.00	1.0000
	6.25	1	39	0	0.025	<.001	1.00	1.0000
	6.5	0	40	0	<.001	<.001		

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

/s/

RONALD H FARKAS
11/18/2011