Zolpidem Tartrate Sublingual Tablets

Edluar™, Intermezzo®

National PBM Abbreviated Drug Review

May 2012

VHA Pharmacy Benefits Management Services,

Medical Advisory Panel, and VISN Pharmacist Executives

The PBM prepares abbreviated reviews to compile information relevant to making formulary decisions. The manufacturer's labeling should be consulted for detailed drug information. VA clinical experts may provide input on the content. Wider field review is not sought. Documents no longer current will be placed in the Archive section.

Executive Summary[1-3, 5, 9-12]

- Zolpidem tartrate sublingual (SL) tablet is a non-benzodiazepine sedative-hypnotic agent that is designed to deliver and facilitate absorption of a portion of the dose through the tissues of the sublingual cavity. Currently, two sublingual zolpidem products are available.

Indication:

- Standard dose zolpidem SL (5 mg and 10 mg) or Edluar™ received FDA approval in 2009 for short-term treatment of insomnia characterized by difficulties with sleep initiation.

- Low dose zolpidem SL (1.75 mg and 3.5 mg) or Intermezzo® received FDA approval in 2011 for as needed treatment of insomnia when middle-of-the-night (MOTN) awakening is followed by difficulty returning to sleep. Low dose zolpidem SL is not indicated for the treatment of middle-of-the-night awakening when the patient has fewer than 4 hours of bedtime remaining.

Efficacy:

- Standard dose zolpidem SL: Two PSG studies (Staner et al. 2010 evaluated 70 primary insomniac patients; Staner et al 2009 evaluated 18 healthy subjects using a post-nap model) have shown that the standard dose zolpidem SL provides a more rapid sleep onset compared to oral zolpidem IR as measured by the objective sleep parameters. The sleep initiation parameter, latency of persistent sleep (LPS), was significantly reduced by 10.28 minutes ($p=0.001$) and 6.11 minutes ($p = 0.034$) with standard dose zolpidem SL 10 mg compared to oral zolpidem IR 10 mg in the primary insomnia and post-nap studies, respectively. In Staner et al. 2010, sleep onset latency (SOL) and latency to stage 1 (ST1L) were shortened by 8.63 minutes ($p<0.01$) and 7.43 minutes ($p<0.01$) with zolpidem SL 10 mg compared to zolpidem IR 10 mg. In Staner et al. 2009, zolpidem SL 10 mg shortened the SOL and ST1L by 5.81 minutes ($p=0.024$) and 6.17 minutes ($p=0.011$), respectively, compared to zolpidem IR 10 mg. Subjective sleep parameters, Leeds Sleep Evaluation Questionnaire (LSEQ) and next day residual sedation, were similar in both formulations of zolpidem (SL and IR).

- Low dose zolpidem SL: Roth et al 2008 conducted a randomized, double-blind, placebo controlled, 3 way cross over study in 5 U.S. sleep laboratories. Eighty subjects with DSM-IV criteria for primary insomnia and a history of prolonged MOTN awakenings completed this study. Low dose zolpidem SL demonstrated a significantly earlier sleep initiation compared to placebo. The LPS after MOTN awakening decreased with zolpidem SL 3.5 mg, zolpidem SL 1.75 mg, and placebo by 9.69 minutes ($p<0.001$), 16.89 minutes ($p<0.001$), and 28.12 minutes, respectively. Mean total sleep time after MOTN awakening (TST_{MOTN}) values were significantly increased in both active treatment arms compared to placebo, ($p<0.001$). Neither doses of zolpidem SL impacted sleep maintenance parameters (i.e., number and duration of awakenings after sleep onset: NAW_{MOTN} and $WASO_{MOTN}$). Patient-reported estimates of sleep onset latency (SOL_{MOTN}) were significantly shorter with both sublingual zolpidem doses compared to placebo ($p<0.001$). Patient-reported estimates of total sleep time ($sTST_{MOTN}$) were significantly longer with both zolpidem sublingual doses compared to placebo (3.5 mg: $p<0.001$; 1.75 mg $p<0.011$). No objective or subjective next day residual sedative effects were seen following awakening in either gender at 4.5 hours after dosing compared to placebo.

Safety:

- Both zolpidem SL formulations and doses were well tolerated and did not induce residual daytime effects. Zolpidem SL is contraindicated in patients with history of hypersensitivity to oral zolpidem and should not be re-challenged.

- Standard dose zolpidem SL: The adverse event profile of standard dose zolpidem SL is comparable to those of the oral zolpidem IR formulations. The most frequent adverse drug events reported with standard dose sublingual zolpidem from the two PSG published trials reported in > 1% of patients were somnolence, fatigue, headache and dysgeusia.

- Low dose zolpidem SL: The most common adverse drug reactions reported in > 1% of patients were headache, nausea, and fatigue. The adverse drug events for low dose zolpidem SL are based on two double-blind placebo-controlled trials (one of the two trials has not been published).

Drug Interactions:

- CNS-depressants (benzodiazepines, opioids, tricyclic antidepressants, alcohol) could potentially enhance the CNS-depressant effects of sublingual zolpidem. The efficacy of sublingual zolpidem may be increased by CYP3A4 inhibitors (ketoconazole) and decreased by CYP3A4 inducers (rifampin).

Monitoring:

- There are no specific laboratory tests recommended.

Dose:

- The dose of zolpidem SL should be individualized. For optimal effect, zolpidem SL tablets should not be administered with or immediately after a meal. The sublingual zolpidem tablet should not be swallowed nor taken with water. Dual use of sublingual zolpidem with other formulations of zolpidem should not be used. Sublingual zolpidem used concurrently with other sedative hypnotics or other medications used to treat insomnia is not recommended.

- Standard dose zolpidem SL: For treatment of insomnia characterized by difficulties with sleep initiation, the recommended dose is 10 mg daily for adults and 5 mg daily for elderly or debilitated patients, and hepatic impairment. The total daily dose should not exceed 10 mg.
    - Dose should be placed under the tongue once daily immediately before bedtime and only when able to stay in bed a full night (7-8 hours) before being active again.

    - Standard dose zolpidem SL is recommended for the treatment of short-term insomnia (i.e. 1-4 weeks). It is recommended to limit the prescription quantity to a 30 day supply with no more than 2 refills and then reassess.

- Low dose zolpidem SL: It is the only zolpidem formulation with gender specific dosing recommendations. For treatment of MOTN awakening followed by difficulty returning to sleep (subtype of maintenance insomnia), the recommended dose is 3.5 mg for adult men and 1.75 mg for adult women, elderly, hepatic impairment, and patients taking concomitant CNS depressants. The total daily dose should not exceed 3.5 mg for men and 1.75 mg for women.
    - Dose should be placed under the tongue once daily as needed after MOTN waking and when ≥ 4 hours of bedtime remain.
    - MOTN does not occur every night. It is recommended to limit prescription quantity to 15/month with no more than 2 refills and then reassess.

Summary:

- Standard dose zolpidem SL improves the onset of sleep compared to zolpidem IR. It is used for the treatment of short-term insomnia characterized by difficulties with sleep initiation. It will have limited use relative to generic immediate-release zolpidem. Oral zolpidem product should be considered first if a non-benzodiazepine sedative-hypnotic agent is desired. Sublingual zolpidem should be reserved for patients who have difficulty swallowing, are unable to swallow, or do not tolerate oral administration.

- Low dose zolpidem SL improves the onset of sleep compared to placebo. It is indicated for as needed treatment of insomnia when middle-of-the-night (MOTN) awakening is followed by difficulty returning to sleep The dose should be taken following MOTN awakenings (not prophylactically at bedtime) and only if the patient has at least 4 hours of sleep remaining.

- Dual use of sublingual zolpidem with other formulations of zolpidem should not be used. Sublingual zolpidem used concurrently with other sedative hypnotics or other medications used to treat insomnia is not recommended.

Introduction[1-10]

The purpose of this abbreviated drug monograph is to evaluate the available evidence of efficacy, safety, and role in therapy for sublingual zolpidem.

Symptoms of insomnia include difficulties initiation, sleep maintenance, early morning awakenings, or unrefreshed sleep.[1] The prevalence of insomnia is reported to be between 20-50% in the general Western population.[2] Most experts agree that the prevalence of insomnia is more common in women, older adults particularly those with depression and chronic medical, or psychiatric problems. A U.S. insomnia cost-of-illness study based on 1995 data reported an estimated annual direct cost of insomnia for non-institutionalized civilian population at $14 billion ($21.4 billion in 2011 dollars), of which approximately $2 billion ($3.1 billion in 2011 dollars) were attributed to medication and the remainder to health care services.[3]

A subtype of sleep maintenance insomnia is middle-of-the-night (MOTN) insomnia. It is characterized by difficulty returning to sleep following a nocturnal awakening. The current classifications from Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and International Classification of Sleep Disorders (ICSD) offer no guidelines to help apply a standard definition for MOTN Insomnia.[4] The proposed revisions for DSM-5 criteria (http://www.dsm5.org/ProposedRevision/Pages/proposedrevision.aspx?rid=65) include “difficulty maintaining sleep, characterized by frequent awakenings or problems returning to sleep after awakenings” and “early-morning awakening with inability to return to sleep” as symptoms for Insomnia Disorder. The release of the final, approved DSM-5 is expected in May 2013.

Nocturnal awakenings are one of the most common sleep disturbances in the general population, and in adults with chronic insomnia.[4-5] Sleep loss of even 1-2 hours per night has shown to impair alertness, concentration, cognitive abilities, memory, mood, and pain threshold.[1] However, many patients with this subtype of insomnia do not have MOTN every night. In a telephone survey consisting of 8,937 U.S. residents subjects (> 18 years of age), 35.5% of a representative sample reported awakenings at least 3 nights per week, of which 43% (15.2% of the total sample) reported difficulty resuming sleep; and 47.9% of those subjects report associated daytime impairment.[4] Using data from this survey, the estimated prevalence of insomnia with associated daytime impairment due to MOTN awakening is 2.1% of the adult U.S. population.[3] Ideally, MOTN sleep disruptions should be managed by linking MOTN dosing with symptom occurrence. Administering low dose zolpidem SL on an as needed basis for MOTN awakening helps to prevent unnecessary drug exposure as compared to nightly prophylactic dosing.[5-7]

On March 13, 2009, standard dose zolpidem SL (Edluar™ 5 mg and 10 mg, by Meda Pharmaceuticals) was FDA approved for short-term treatment of insomnia characterized by difficulties with sleep initiation. On November 23, 2011, low dose zolpidem SL (Intermezzo® 1.75 mg and 3.5 mg, by Transcept Pharmaceuticals) was FDA approved for as needed treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep. Low dose zolpidem SL (Intermezzo®) is not indicated for the treatment of MOTN insomnia when the patient has fewer than 4 hours of bedtime remaining before the planned time of waking.[3, 8-11]

Pharmacology/Pharmacokinetics[1, 3, 9-11]

Mechanism of Action: Zolpidem, the active moiety of zolpidem tartrate, is a hypnotic agent with a chemical structure unrelated to benzodiazepines, barbiturates, or other drugs with known hypnotic properties. It shares some of the pharmacological properties of the benzodiazepines (BZDs). However, due to its higher affinity to the

α_1-$GABA_A$ receptor, less myorelaxant and anticonvulsant properties are observed with no disturbance on sleep stage 3 and 4 compared to BZDs.[1, 9]

Absorption: Sublingual zolpidem tablet is designed for transmucosal delivery of zolpidem. It disintegrates in the sublingual cavity and is rapidly absorbed after administration. Standard dose zolpidem SL is bioequivalent to oral zolpidem IR with respect to Coax and AUC. A median Tax of 82 minutes (range: 30-180 min) and a mean Tax range of 35-75 minutes occurred following administration of zolpidem SL 10 mg and zolpidem SL 3.5 mg, respectively. Low dose zolpidem SL has a binary (bicarbonate-carbonate) buffer system that facilitates sublingual absorption of zolpidem.[3, 9-11]

Distribution: Based on data obtained with oral zolpidem, the total protein binding was found to be 92.5% ± 0.1% and 93% ± 0.1% for standard dose zolpidem SL (5 mg, 10 mg) and low dose zolpidem SL (1.75 mg, 3.5 mg), respectively. It remained constant, independent of concentration between 40 ng/mL and 790 ng/mL.[3, 9-11]

Metabolism: Based on data obtained with oral zolpidem, sublingual zolpidem is converted to inactive metabolites that are eliminated primarily by renal excretion.[3, 9-11]

Elimination: When standard dose zolpidem SL is administered as a single 5 mg or 10 mg dose in healthy adult subjects, the mean zolpidem elimination half-life was 2.85 hours and 2.65 hours, respectively.[9-10] After administration of low-dose zolpidem SL 3.5 mg, women cleared zolpidem tartrate from the body at a lower rate than men (2.7 mL/min/kg and 4.0 mL/min/kg, respectively). Table 2 illustrates low dose zolpidem SL, when administered at the same dose in both gender, the plasma AUC and Cmax parameters were approximately 45% higher in women than men.[3,11]

Table 1: Pharmacokinetic Parameters for Zolpidem Sublingual[9, 11]

	Standard dose zolpidem SL (5 mg, 10 mg)	Low dose zolpidem SL (1.75 mg, 3.5 mg)
Elimination half-life (hr)	2.65[a] (range: 1.75-3.77)	2.5[b] (range 1.4-3.6)
T_{max} (min)	82[c] (range: 30-180)	35-75
C_{max} (ng/mL)	106[c] (range; 52-205)	77[d] in women; 53[d] in men
Plasma Protein Binding	92.5% ± 0.1%	93% ± 0.1%
Metabolism[e]	Hepatic methylation and hydroxylation via CYP3A4 (~60%), CYP2C9 (~22%), CYP1A2 (~14%), CYP2D6 (~3%), CYP2C19 (~3%) to inactive metabolites	Hepatic methylation and hydroxylation via CYP3A4 (~60%), CYP2C9 (~22%), CYP1A2 (~14%), CYP2D6 (~3%), CYP2C19 (~3%) to inactive metabolites
Food Effect	Food decreased the mean AUC and Cmax of zolpidem SL 10 mg by 20% and 31%, respectively, while median Tmax was prolonged by 28% (from 82 to 105 min)[f]	Food decreased the overall AUC and Cmax of zolpidem SL 3.5 mg by 19% and 42%, respectively, and increased Tmax to nearly 3 hours[g]
Elimination	Renal (75%)	Renal (75%)

a. Based on a single dose of zolpidem SL 10mg in healthy adults. $t_{1/2}$ is 2.85 hours (range: 1.57-6.73) after a single dose of zolpidem SL 5 mg
b. Based on a single dose of zolpidem SL 3.5 mg
c. Based on a single dose of zolpidem SL 10 mg in 18 healthy adults (18-65 year of age)
d. Based on zolpidem SL 3.5 mg dose in healthy volunteers (21-45 years of age)
e. Based on data obtained with oral zolpidem; UpToDate
f. Studied in 18 healthy volunteers comparing standard dose zolpidem SL 10 mg administered fasting or within 20 minutes after a high fat meal
g. Studied in 36 healthy adults (58% male), aged 19-64 years (mean, 34 years), comparing a single dose of zolpidem SL 3.5 mg administered 30 minutes after a standard high fat meal

Table 2: Gender Specific Mean (SD)* Pharmacokinetic Parameters of Low Dose Sublingual Zolpidem[3]

	Zolpidem SL 1.75 mg		Zolpidem SL 3.5 mg	
	Women (n=11)	**Men (n=13)**	**Women (n=11)**	**Men (n=13)**
$AUC_{0\text{-}inf}$ (ng·hr/mL)	151.36 (61.54)	104.73 (35.04)	295.6 (105.66)	197.69 (72.43)
C_{max} (ng/mL)	37.47 (11.10)	27.68 (7.5)	77.13 (23.71)	53.15 (14.29)

* SD (Standard Deviation)

Table 3: Considerations in Special Populations[3, 9-11]

	Standard dose zolpidem SL	Low dose zolpidem
Dose in Elderly	5 mg	1.75 mg
Dose in Hepatic Impairment	5 mg	1.75 mg
Dose in Renal Impairment	No dosage adjustment is necessary	No dosage adjustment is necessary
Hemodialyzable	No	No

Pregnancy Category	C	C
Children	Not recommended under the age of 18	Not recommended under the age of 18

FDA Approved Indication

Table 4: Sublingual Zolpidem Indications[3, 9-11]

	FDA Approved Indications	Off-Label Indications
Zolpidem SL 5 mg, 10 mg	Short-term treatment of insomnia characterized by difficulties with sleep initiation.	None
Zolpidem SL 1.75 mg, 3.5 mg	Use as needed for the treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep. Limitation of Use: Not indicated for the treatment of middle-of-the-night awakening when the patient has fewer than 4 hours of bedtime remaining	None

Current VA National Formulary Alternatives

Currently, zolpidem tartrate IR is the only non-benzodiazepine sedative-hypnotic agent listed on the VA National Formulary.

Dosage and Administration[3, 9-11]

Dual use of sublingual zolpidem with other formulations of zolpidem is not recommended. Sublingual zolpidem used concurrently with other sedative hypnotics or other medications used to treat insomnia is not recommended.

Standard dose zolpidem SL: The initial and maximum dose is 10 mg daily in adults. Initial dose should be adjusted to 5 mg daily in the elderly or debilitated patients, and patients with hepatic impairment. It is to be taken immediately before patients get in bed and only when they are able to stay in bed a full night (7-8 hours) before being active again. Do not administer with or immediately after a meal.[9-10] Standard dose zolpidem SL is recommended for the treatment of short-term insomnia (i.e. 1-4 weeks). It is recommended to limit the prescription quantity to a 30 day supply with no more than 2 refills and then reassess.

Low dose zolpidem SL: The initial and maximum dose is 1.75 mg and 3.5 mg in women and men, respectively. Initial dose should be adjusted to 1.75 mg in the elderly, patients with hepatic impairment, and patients taking concomitant CNS depressant. Low dose zolpidem SL is not to be taken when patients have less than 4 hours of bedtime remaining before the planned time of waking. For optimal effect, do not administer with or immediately after a meal or with alcohol.[3, 11]

Efficacy

Summary of Standard Dose Zolpidem SL Efficacy Findings[2, 12]

Staner et al. 2010 conducted a randomized, double-blind, two-period, crossover, multi-center study comparing the hypnotic effects of a single dose of zolpidem SL 10 mg and zolpidem IR 10 mg. Seventy-three subjects with primary insomnia (42 females – mean age 45.5±9.5 years; 31 males – mean age 35.7±11 years) were randomized from eight centers located in France, Belgium, and Russia. Seventy subjects completed the study; three were excluded from the randomization. The polysomnography (PSG) results demonstrated that zolpidem SL 10 mg significantly shortened all three objective sleep initiation parameters (LPS, SOL, and ST1L), compared to zolpidem IR 10 mg. The LPS, SOL, and ST1L were reduced by 10.28 minutes ($p=0.001$), 8.63 minutes ($p<0.01$), and 7.43 minutes ($p<0.01$), respectively. Zolpidem SL 10 mg increased sleep efficiency (SE) by 1.56% ($p<0.05$), compared to zolpidem IR 10 mg. Other sleep continuity parameters (TST and WASO) were comparable between the sublingual and oral formulations. Subjective sleep and next day residual effects, from patient-reported LSEQ, VAS, DSST, and MCRT were comparable between zolpidem SL 10 mg and zolpidem IR 10 mg. Both routes of administration (sublingual and oral) were well tolerated.[2]

Staner et al. 2009 conducted an open, randomized, three-period, crossover, single-center study in 21 healthy volunteers (17 females, 4 males, age 26.7±5.3 years) utilizing a post-nap model of insomnia. Treatment arms included zolpidem SL 5 mg, zolpidem SL 10 mg, and zolpidem IR 10 mg. Eighteen subjects completed the study. Three subjects discontinued the study due to swallowing the sublingual tablet, nap failure, and lack of regular bedtimes. Each study period consisted of two consecutive recording nights. On the day between baseline and the

post-nap treatment night, subjects napped at least 30 minutes of cumulative sleep stages 1-4 or REM from 4-6 pm. The primary objective was to evaluate the efficacy of single doses of zolpidem SL 5 mg, zolpidem SL 10 mg, and zolpidem IR 10 mg on objective sleep latency (LPS), measured by PSG. The results demonstrated that zolpidem SL 10 mg significantly shortened all three objective sleep initiation parameters (LPS, SOL, and ST1L), compared to zolpidem IR 10 mg. The LPS, SOL, and ST1L were reduced by 6.11 minutes (~30% improvement); p=0.034), 5.81 minutes (p=0.024), and 6.17 minutes (p=0.011), respectively. Zolpidem SL 5 mg and zolpidem IR 10 mg did not reveal any significant differences for the three sleep initiation parameters. No significant treatment effects were evident for sleep maintenance parameters (TST, WASO, SE). Subjective sleep and next day residual effects, from patient-reported LSEQ, VAS, DSST, CFFT, and MCRT were comparable between zolpidem SL 5 mg, zolpidem SL10 mg, and zolpidem IR 10 mg. Both routes of administration (sublingual and oral) and doses were well tolerated.[12]

Summary of Low Dose Zolpidem SL Efficacy Findings[3, 5]

Roth et al. 2008 conducted a randomized, double-blind, placebo-controlled, 3-way crossover study conducted in 5 US sleep laboratories. It evaluated the efficacy and safety of low dose zolpidem SL when taken during a scheduled MOTN awakening. Sleep parameters were assessed by PSG and subjective post-sleep questionnaires. The study included 82 healthy adult subjects (58 females, 24 males, mean age 45.9 years: range 19-64) with an established diagnosis of DSM-IV primary insomnia and at least a 4-week history of prolonged MOTN awakenings. Subjects were required to have MOTN awakenings at least 3 nights per week with mean latency to fall back to sleep ≥ 30 minutes post-awakening. Treatment arms included zolpidem SL 1.75 mg, zolpidem SL 3.5 mg, and placebo. Latency to persistent sleep (LPS_{MOTN}) was the primary endpoint and objective total sleep time after a scheduled middle-of-the-night awakening (TST_{MOTN}) was the principal secondary endpoint. Both doses of low dose zolpidem SL (1.75 mg and 3.5 mg) resulted in statistically significant decreases in latency to persistent sleep and improvement in total sleep time, when compared with placebo. Secondary efficacy endpoints (TST_{MOTN}, SE_{MOTN}, SOL_{MOTN}, $sTST_{MOTN}$, LPS_{MOTN}) also achieved statistical significance. Neither dose showed next-morning impairment on the Digit Symbol Substitution Test (DSST) after the Morning Sleep Questionnaire or on the ratings of sleepiness using Visual Analog Scale (VAS) four hours after dose administration.[5]

In a randomized, double-blind, placebo-controlled study of 295 non-elderly outpatients with history of primary insomnia and MOTN awakenings were randomly assigned to receive either low dose zolpidem SL 3.5 mg or placebo on an as needed basis over a 4-week period. Patients were assessed via a telephone interactive voice response system (IVRS). Patients who received zolpidem SL 3.5 mg once a night prn reported a significantly shorter latency to sleep onset (primary endpoint) over the 4-week study period compared to those who received placebo (38.2 minutes and 56.4 minutes, respectively (p<0.001)). During the treatment period, patients randomized to low dose zolpidem SL took the drug during the night on 62% of study nights. Patients demonstrated no rebound during nights they did not take study drug. Drug utilization did not increase over the 4-week treatment period in the outpatient study (unpublished data. Data on file with company).[3]

Adverse Events (Safety Data)[1-3, 5, 9-11]

Types of adverse events reported for patients treated with sublingual zolpidem were consistent with the adverse event profile of oral zolpidem. Long-term safety profile for sublingual zolpidem is currently not available.

Zolpidem is classified as a Schedule IV controlled substance by federal regulation because it can be abused or lead to dependence. Cases of abuse and dependence have been reported with oral zolpidem in patients with previous history of substance abuse and/or concomitant psychiatric illness. It is not known whether sublingual zolpidem have a different tolerance withdrawal reaction, abuse, and dependence potential profile than oral formulation.[1]

Next-Day Residual Effects[6]

Roth et al., 2008 conducted a single-dose, randomized, double-blind, placebo controlled, daytime, cross-over study with sublingual zolpidem 1 mg, 1.75 mg, and 3.5 mg in 24 healthy non-smoking volunteers, (range 21-44 years of age) with a mean BMI of 24.9 and evaluated any residual effects of low dose sublingual zolpidem not only pre-dose but also several intervals up to 5 hours post-dose. Patients qualified for randomization if their 7-day diaries reported a mean weekly latency to sleep onset of ≤ 30 minutes, a mean weekly total time in bed of ≥ 7 hours, and a stable bedtime pattern. Psychomotor performance and sedative effects of low dose zolpidem SL

were measured using objective pharmacodynamic tests including Digit Symbol Substitution Test (DSST), Choice Reaction Test (CRT), and Word Recall Test. Residual effects in the morning were assessed by using the subjective self-rating Visual Analog Scale (VAS). No significant performance differences were observed during the pre-drug performance for any of the endpoints. The DDST scores indicated significant psychomotor impairment for both 3.5 mg and 1.75 mg sublingual zolpidem as early as 20 minutes post-intake compared to placebo. The significant impairment lasted up to 60 minutes and 90 minutes post-dose for the 1.75 mg and 3.5 mg doses, respectively. Compared to placebo, no difference in the DSST scores was seen for both strengths 4-5 hours post dose. Zolpidem SL 3.5 mg impacted all outcome measures of the other pharmacodynamic tests at different time periods. Fine motor activity as measure by SCT was impaired 1.5 hours and 1 hour with 3.5 mg and 1.75 mg post dose, respectively. Compared to placebo, memory (immediate free recall) was impaired by zolpidem SL 3.5 mg at 20 minutes post-dose and undetectable 1 hour later. No measurable effect was observed with the zolpidem SL 1.75 mg dose. Self-ratings of significant sedation by the VAS from 20 minutes through 2 hour post-drug at the 1.75 mg and 3.5 mg dose levels compared to placebo. The ratings were different from placebo up to 3 hours, but were no longer statistically significantly different, primarily due to increased sedation rating in the placebo group. Overall, the maximum impairment of sublingual zolpidem 1.75 mg and 3.5 mg for the measured parameters ranged from 20 minutes to 2 hours post-dose compared to placebo.

Contraindications[3, 9-11]

Sublingual zolpidem is contraindicated in patients with known hypersensitivity to zolpidem tartrate. Observed reactions include anaphylaxis and angioedema, patients who developed such reactions should not be re-challenged with the drug.

Warnings and Precautions[3, 9-11]

CNS depressant effects: Alertness and motor coordination may be impaired. Due to the potentially additive effects, sublingual zolpidem dosage adjustments may be necessary when administered with CNS depressants. Sublingual zolpidem should not be taken with alcohol. Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination such as operating machinery or driving a motor vehicle after ingesting the drug.

Evaluate for co-morbid diagnoses: Failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated.

Severe anaphylactic/anaphylactoid reactions: Angioedema and anaphylaxis have been reported. Do not re-challenge if such reactions occur.

“Sleep-driving” and other complex behaviors: Driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event have been reported. Risk increases with dose and concomitant use with other CNS depressants and alcohol. Immediately evaluate any new onset behavioral changes.

Depression: Worsening of depression or suicidal thinking may occur. Prescribe the least number of tablets feasible to avoid intentional overdose.

Respiratory Depression: Sedative-hypnotics have the capacity to depress respiratory drive, precautions should be taken if zolpidem is prescribed to patients with compromised respiratory function.

Withdrawal Effects: There have been reports of withdrawal signs and symptoms following the rapid dose decrease or abrupt discontinuation of zolpidem. Monitor patients for tolerance, abuse, and dependence.

Look-Alike/Sound-Alike (LA/SA) Error Risk Potential

As part of the Joint Commission Medication Management standard, LA/SA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LA/SA information from three data sources (Lexi-Comp, First DataBank, and ISMP Confused Drug Name List), the following drugs may cause LA/SA confusion.

Table 5: LA/SA

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment

Zolpidem SL	Lorazepam Zaleplon	None	None	Zolpidem (regular) Zyloprim Zolmitriptan
Edluar 5 mg, 10 mg	None	None	None	Edurant
Intermezzo 1.75 mg, 3.5 mg	None	None	None	None

Drug Interactions[3,9-11]

Like other sedative-hypnotics, sublingual zolpidem has CNS depressant effects. Co-administration with other CNS depressants (e.g. benzodiazepines, opioids, tricyclic antidepressants, alcohol) increases the risk for CNS depression, abnormal thoughts and behavior (e.g. more outgoing or aggressive behavior than normal, confusion, agitation, hallucinations, worsening of depression, and suicidal thoughts or actions), and complex behavior (e.g. sleep-driving, making and eating food, talking on the phone, having sex, and sleep-walking) with amnesia for the event.

Some compounds known to inhibit CYP3A4 may increase the efficacy of zolpidem. The effect of other P450 enzymes on the pharmacokinetics of zolpidem is unknown. The pharmacokinetics and pharmacodynamics of zolpidem were not altered by cimetidine, ranitidine, digoxin, and warfarin. Imipramine and Chlorpromazine may produce an additive effect of decreased alertness and/or psychomotor performance. These drugs did not show any significant pharmacokinetic interaction.

Table 6: Zolpidem Drug Interactions[3,9-11]

Drugs	Effects
CNS depressants (including alcohol)	May produce additive CNS depressant effects
Rifampin (CYP3A4 inducer)	May decrease the efficacy of zolpidem
Ketoconazole (CYP3A4 inhibitor)	May increase the efficacy of zolpidem
Imipramine	May decrease alertness
Chlorpromazine	May impair alertness and psychomotor performance

Pharmacoeconomic Analysis

There are no specific economic models for sublingual zolpidem products.

Conclusions

Sublingual zolpidem has a rapid onset of action for sleep initiation. Long-term efficacy and safety data are not available. The use of sublingual zolpidem with other formulations of zolpidem is not recommended. Sublingual zolpidem used concurrently with other sedative hypnotics (including other zolpidem products) or other medications used to treat insomnia at bedtime or during the middle of the night is not recommended. Zolpidem SL tablet should be placed under the tongue. The tablet should not be taken with water and should not be swallowed. Zolpidem SL should not be administered with or immediately after a meal as food may delay the onset of hypnotic effects.

Standard dose zolpidem SL is indicated for short-term treatment of insomnia characterized by difficulties with sleep initiation. The recommended dose is 10 mg daily for adults. Dose adjustment is necessary for the elderly, debilitated, and hepatic impairment patients. Patients should have a full 7 to 8 hours of sleep before being active again. Sleep maintenance and safety profiles are comparable to oral zolpidem. Oral zolpidem product should be considered first if a non-benzodiazepine sedative-hypnotic agent is desired. Sublingual zolpidem should be reserved for patients who have difficulty swallowing, are unable to swallow, or do not tolerate oral administration. Standard dose zolpidem SL is recommended for the treatment of short-term insomnia (i.e. 1-4 weeks). It is recommended to limit the prescription quantity to a 30 day supply with no more than 2 refills.

Low dose zolpidem SL is the first non-benzodiazepine sedative-hypnotic that is FDA approved for treatment of insomnia characterized by difficulty returning to sleep after middle-of-the-night (MOTN) awakening. Women clear zolpidem SL at a slower rate than men. The recommended dose is 1.75 mg for women and 3.5 mg for men. Dose adjustment is necessary for elderly, hepatic impairment, and patients taking concomitant CNS depressant. Patients should only take this product if they have difficulty returning to sleep after MOTN awakening and have at least 4 hours of bedtime remaining before the planned time of awakening.

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Prepared: May 2012
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Appendix A: Clinical Trials

Table 1: Standard Dose Zolpidem SL and Zolpidem IR for Primary Insomnia

<table>
<tr><th>Trial/ Objective/Funding</th><th>Study Design</th><th>Results and Conclusions</th></tr>
<tr>
<td>Staner et al. 2010[2]

Objective: To compare the hypnotic effects (sleep induction: LPS, SOL, and ST1L) of a single dose of a sublingual zolpidem 10 mg and oral zolpidem 10 mg by PSG in DSM-IV primary insomnia patients.

This study was funded by Orexo AB</td>
<td>Design: R, DB, two-period cross-over multi-center international study (conducted in 10 study sites; 8 centers recruited subjects).

Medical Screening Phase: medical and psychiatric history, physical examination, 12-lead ECG, clinical lab tests, alcohol and drug screening.

2-day PSG Screening Phase: Respiratory and leg electromyograms to exclude apnea/hypopnea index > 10/hour or with a periodic leg movement arousal index > 10/hour; mean latency to LPS > 30 minutes with no LPS < 20 minutes; TST for both nights < 6.5 hour and WASO > 30 minutes.

Two 3-day Treatment Periods: each with two successive PSG recording nights. A washout period of 7-14 days separated the two treatment periods.

Inclusion:
• Age 18-65 with DSM-IV diagnosis of primary insomnia;
• Regular bedtime hours between 10 pm-1 am and no shift work or flight across more than 3 time zones within 1 week prior to screening;
• Women must not be lactating and, if of child-bearing potential, must use appropriate birth control for the entire duration of the study;
• BMI 18-30 and absence of a current unstable significant medical condition;
• No history of seizures, sleep apnea, COPD, RLS, periodic leg movement syndrome, fibromyalgia, cognitive disorder, mental retardation, schizophrenia, or bipolar disorder;
• No history of alcohol or drug abuse within the past 12 months;
• No history of other psychiatric disorder (anxiety, depression) within past 6 months;
• No use of drugs or supplements known to affect sleep/wake function; nor of CNS medication within 1 week prior to screening
• Caffeine consumption < 500 mg/day and alcohol consumption < 40 gm/day;
• Nicotine consumption < 10 cigarettes/day or equivalent/day and subject agreed to stop nicotine during PSG screening phase and the</td>
<td>Participants: One hundred fifty-eight subjects with DSM-IV diagnosis of primary insomnia were screened. Seventy-three (31 m, mean age 35.7±11 yr; 42 f, mean age 45.5±9.5 yr) were randomized; 70 completed the study. Three subjects were excluded from the study after randomization, (1 patient with 2 serious AE; 2 patients had delayed start time of PSG recording).

Efficacy:
Primary and secondary endpoints (Mean ± SD) on Objective Sleep Parameters in Primary Insomnia Patients n=70
<table>
<tr><th colspan="2">Sleep Parameters[a]</th><th>Baseline</th><th>Zolpidem SL 10 mg</th><th>Zolpidem IR 10 mg</th><th>Mean Treatment Differences</th></tr>
<tr><td rowspan="3">Sleep Initiation (min)</td><td>LPS</td><td>84.54±40.35</td><td>19.76±15.55</td><td>30.06±23.48</td><td>-10.28(p=0.001)</td></tr>
<tr><td>SOL</td><td>72.3±39.32</td><td>17.66±13.37</td><td>26.31±22.72</td><td>-8.63 (p<0.01)</td></tr>
<tr><td>ST1L</td><td>61.07±34.64</td><td>13.94±12.67</td><td>21.35±20.3</td><td>-7.43 (p<0.01)</td></tr>
<tr><td rowspan="3">Sleep Continuity (min)</td><td>TST</td><td>324.29±46.52</td><td>432.06±29.3</td><td>424.72±34.42</td><td>7.22</td></tr>
<tr><td>WASO</td><td>84.08±36.16</td><td>30.87±27.79</td><td>29.82±26.8</td><td>1.13</td></tr>
<tr><td>SEI (%)</td><td>67.47±9.65</td><td>89.9±6.09</td><td>88.33±6.98</td><td>1.56 (p<0.05)</td></tr>
<tr><td rowspan="6">Sleep Architecture</td><td>TTA (min)</td><td>153.94±46.43</td><td>45.8±29.23</td><td>53.41±33.57</td><td>-7.52 (p<0.05)</td></tr>
<tr><td>ST1 (min)</td><td>22.08±8.81</td><td>23.06±8.5</td><td>23.15±8.18</td><td>-0.06</td></tr>
<tr><td>ST2 (min)</td><td>182.56±46.04</td><td>253.09±35.98</td><td>242.38±34.09</td><td>10.54 (p<0.05)</td></tr>
<tr><td>SWS (min)</td><td>51.65±25.19</td><td>71.91±32.69</td><td>73.6±29.96</td><td>-1.51</td></tr>
<tr><td>REM (min)</td><td>70.44±19.64</td><td>86.74±24.72</td><td>88.31±20.64</td><td>-1.73</td></tr>
<tr><td>RSL (min)</td><td>81.81±40.77</td><td>95.34±40.7</td><td>87.98±40.78</td><td>7.38</td></tr>
</table>
[a] Sleep initiation endpoints were tested at the 5% alpha level to assess superiority whereas sleep continuity endpoints were tested for non-inferiority at the alpha level of 2.5%.

Subjective sleep ratings of “getting to sleep” and “behavior following awakening” did not reach statistical significance for sublingual zolpidem compared to oral zolpidem as documented with LSEQ scale. Next-day residual effects: No significant differences were noted between subjects taking sublingual and oral formulations of zolpidem when rating feelings of alertness, contentedness and calmness (with VAS). Likewise, no differences were seen between the two formulations using MCRT and DSST (data not shown). Patients on zolpidem SL 10 mg exhibited a lower flicker fusion threshold on the descending runs on the CFFT (p<0.05) compared to zolpidem IR 10 mg; no difference on the ascending runs was observed.

Results:
• Compared to oral formulation (zolpidem IR 10 mg), zolpidem SL 10 mg significantly shortened all sleep initiation endpoints (LPS, SOL, and ST1L).
• The LPS was reduced by 10.3 minutes (34%; (95% CI: -4.3 min to -16.2 min, p=0.001); and SOL and STIL by 9.6 minutes (95% CI 3 min to -14.2 min, p<0.01) and 7.4 minutes (95% CI: -2.4 min to -12.5 min, p<0.01, respectively.
• Zolpidem SL 10 mg was at least as good as zolpidem IR 10 mg on sleep maintenance parameter, TST. Non-inferiority limit was not achieved for the duration of WASO.
• Other sleep continuity and sleep architecture parameters such as sleep efficiency index, total time awake, time spent in stage 2 and time spent in non REM sleep were significantly (p<0.05) improved with sublingual zolpidem compared to oral zolpidem.
• Subjectively, the ease to fall asleep as determined by subscale of the LSEQ was better but not statistical significant</td>
</tr>
</table>

	two treatment periods **Treatment**: 3-day treatment period including with two PSG treatment night with zolpidem SL 10 mg or zolpidem IR 10 mg • Administered at least 3 hours after last food intake just before lights off at 11 pm. • All PSG recordings were made for 8 hours with fixed bedtime hours (11 pm to 7 am). Subjective sleep and next-morning residual effects were assessed 30 minutes after final awakening (~7:30 am on day 2). A washout period of 7-14 days separated the two treatment periods. **Assessment**: **Primary Endpoints:** • Objective sleep initiation: LPS (primary); ST1L, SOL (secondary) • Objective sleep continuity (maintenance): TST, WASO (tested for "at least as good as") **Secondary Endpoints**: • Objective Sleep architecture: TTA, ST1, ST2, SWS, REM, RSL • Subjective Sleep: LSEQ; (monitor subjectively perceived changes in sleep) • Next-Day Residual Effects: VAS (assessed subjective feelings such as alertness, contentedness, and calmness), DSST (assessed the capacity for attention and concentration), and required information processing (sensorial information recognizing), CFFT, MCRT performed 30 minutes after awakening form treatment night • Assess tolerability and safety of study treatments	• Next-day residual effects with zolpidem SL were comparable to that of zolpidem IR as indicated by LSEQ; Bond and Lader visual analog scale (assessment of alertness, contentedness and calmness) or by objective findings on vigilance and psychomotor performance (critical flicker frequency test and multiple choice reaction time test) as well as on DSST (attention and concentration capacities) . **Safety**: Both routes of administration (sublingual and oral) were well tolerated with similar AE that were mild to moderate in severity. Eighteen AEs occurred in 16 patients with oral zolpidem and 13 AE occurred in 11 patients with sublingual zolpidem. Most common AEs were somnolence (3) and dysgeusia (2); and nausea (4), dysgeusia (2), somnolence (2), and dizziness (2) for zolpidem SL 10 mg and zolpidem IR 10 mg, respectively. Despite a negative urinary pregnancy test on day 1 of study, one subject (45 yr) was found to be pregnant during the first treatment period after administration of zolpidem IR 10 mg. This subject was withdrawn from the study before the start of the second treatment and later experienced a miscarriage. This was defined as a serious AE per study protocol, but was considered unrelated to the study treatment. **Conclusions:** Zolpidem SL 10 mg had a faster sleep induction effect but did not differ in terms of the sleep maintenance parameters when compared to zolpidem 10 mg in patients with primary insomnia. Next day residual effects with zolpidem SL were similar to zolpidem IR. **Quality Assessment:** (Good) although may not be generalized to VA population **Study Critique**: • **Strength**: R, DB study with head-to-head comparisons; primary endpoints achieved statistical significance; evaluated objective and subjective sleep parameters. • **Weakness**: no placebo comparison; study was performed in the frame of an experimental trial with stringent selection criteria • **Limitations**: Preparation and publication of article was supported by Orexo AB. Three of the authors were employees of supporting company. One author received financial support from company. Four authors (including the primary one) were employees of a contract research organization that received funding from company.

Table 2: Standard Dose Zolpidem SL and Zolpidem IR in Healthy Volunteers for Post-Nap Insomnia

Trial/ Objective/Funding	Study Design	Results and Conclusions
Staner et al. 2009[12] **Objective**: To evaluate the efficacy of single doses of sublingual zolpidem (5 mg and 10 mg) and	**Design**: open, randomized, 3-period, crossover, single-center study **Screening**: Screening involved medical and psychiatric history, physical examination, 12-lead resting ECG, standard EEG, clinical lab exam, and urine drug screening. **Inclusion**:	**Participants**: Twenty-seven healthy subjects enrolled in the study, six were excluded prior to any treatment for use of prohibited medication (1), consent withdrawal (1), biological abnormalities (2), and nap failure (2). Twenty-one subjects (4 m; 17 f; mean aged 26.7±5.3 yr) were randomized in the study; 18 subjects completed the study. Three discontinued the study due to swallowing SL tablet as oral tablet (1), nap failure (1), and lack of regular bedtimes according to Actigraph™ recordings (1). Table 1: Primary Objective Seep Initiation Parameters effects of Single Doses of zolpidem SL and IR in Healthy Volunteers (means ± SD) using Post-Nap Insomnia Model

Sleep Parameters	Zolpidem SL 5 mg	Zolpidem SL 10 mg	Zolpidem IR 10 mg	Difference between zolpidem SL 10 mg and

oral zolpidem (10 mg) with regard to LPS in a post-nap model of insomnia.

This study was funded by Orexo AB

- Nonsmokers with a non-excessive consumption of alcohol (≤ 40 gm/day) or caffeine-containing beverages (< 6 cups/day); and
- Regular bedtime hours (sleep time:10 pm-midnight, wake time: 6-8 am).

Exclusion:

- Evidence of psychiatric, neurological, cardiac, renal, hepatic, or endocrine disease;
- Sleep disorders (sleep apnea & periodic limb movements); extreme chronotypes;
- Concomitant medications (must be withdrawn at least 6 weeks for CNS acting meds and at least 2 weeks for other meds before study inclusion);
- Lack regular bedtime (outside of the time frame of 10 pm-midnight to 6-8 am);
- Unsuccessful naps (< 30 min of sleep in stages 1-4 or REM; subjects napped from 4-6 pm).

Treatment: Zolpidem SL 5 mg, zolpidem SL 10 mg, or zolpidem IR 10 mg

- Administered at 10:30 pm ± 30 minutes under the supervision of clinical staff and 30 minutes before starting PSG recordings on the post-nap nights.
- Subjects slept in a darkened and sound-attenuated room in the sleep laboratory during three consecutive study periods that were each separated by at least one week of washout period.

Assessment:

- **Primary Endpoints**: Objective: Sleep initiation: LPS (primary) SOL, and ST1L (secondary)
- **Secondary Endpoints**: Objective: Sleep Latency: SOL, ST1L; Sleep maintenance: TST, WASO, SE; Sleep architecture: ST1, ST2, ST3, ST4,SWS, REM, RSL; Subjective Sleep: LSEQ; Next-Day Residual Effects: VAS, DSST, CFFT, MCRT
- Next day residual effects and the safety of single doses of sublingual zolpidem and oral zolpidem in healthy

				zolpidem IR 10 mg (p value)
LPS (min)	19.53±11.49	12.79±9.91	18.36±11.29	-6.11±2.76 (0.034)
SOL (min)	20.86±11.23	14.17±7.65	19.97±11.16	-5.81±2.45 (0.024)
ST1L (min)	16.56±9.1	10.5±7.03	16.67±10.17	-6.17±2.27 (0.011)

Table 2: Secondary effects of zolpidem SL and IR on sleep maintenance, sleep architecture (means ± SD)

Sleep Parameters		Zolpidem SL 5 mg	Zolpidem SL 10 mg	Zolpidem IR 10 mg
Objective Variables	TST (min)	423±39.8	430.2±28.7	434.4±20.8
	WASO (min)	29.42±26.78	24.67±22.01	24.28±16.99
	SE (%)	88.13±8.33	89.75±6.13	90.35±4.03
	ST1 (min)	14.47±7.35	12.97±6.37	13.89±5.98
	ST2 (min)	245±36.3	253.1±27	243.7±21.2
	ST3 (min)	15.72±8.43	14.86±7.22	14.39±7.05
	ST4 (min)	53.83±22.06	60.92±18.18	65.72±20.13
	SWS (min)	69.56±25.45[a]	75.78±18.44	80.11±18.81
	REM (min)	93.97±23.49[a]	88.33±21.69	96.64±17.94
	RSL (min)	72.53±25.6	81.64±26.83	91.75±27.23
Subjective Variables (LSEQ)[b]	Getting to sleep	59.81±13.26	67.78±15.35	57.8±13.64
	Quality of sleep	58.69±21.82	65.28±18.86	63.19±13.64
	Awakening from sleep	51.53±14.36	53.14±20.59	49.36±16.59
	Behavior following sleep	55.02±15.1	52.71±19.62	53±16

a. Significant difference between zolpidem SL 5 mg and zolpidem IR 10 mg were evidenced in SWS and REM (p<0.05).
b. LSEQ Scale: 0 (very bad) to 100 (very good)

Results:

- Compared to oral formulation (zolpidem IR 10 mg), zolpidem SL 10 mg significantly shortened all sleep initiation endpoints (LPS, SOL, and ST1L).
- The LPS was reduced by 6.11 minutes (p=0.034); and both SOL and ST1L by 6 minutes, p=0.024 and p=0.011 with zolpidem SL 10 mg compared to zolpidem IR 10 mg, respectively.
- No other variables showed clinically relevant differences between the treatments.
- Zolpidem SL 5 mg did not differ significantly from zolpidem IR 10 mg on variables measuring ease to get asleep.
- Next-Day Residual Effects (VAS, DSST, CFFT, and MCRT) were comparable between zolpidem SL 5 mg, zolpidem SL10 mg, and zolpidem IR 10 mg.

Safety: None of the subjects withdrew due to safety reasons. Both routes of administration (sublingual and oral) were well tolerated. The most frequent adverse events reported were mild to moderate in severity and resolved spontaneously. The most frequent AE were somnolence, headache and fatigue which are expected events with zolpidem. No other relevant changes in vital signs, ECGs, laboratory tests or physical examination were reported.

Adverse Events	Zolpidem SL 5 mg	Zolpidem SL 10 mg	Zolpidem IR 10 mg
Somnolence	3	1	1
Headache	0	3	0
Fatigue	2	0	0

Conclusions: Zolpidem SL 10 mg displayed sleep-inducing effects that were approximately six minutes faster than zolpidem IR 10 mg in healthy volunteers in post-nap model of insomnia. Neither the two doses of sublingual zolpidem nor oral zolpidem had any residual daytime effects. Both doses of sublingual zolpidem as well as oral zolpidem were well tolerated.

Quality Assessment: (Fair) although may not be generalized to VA outpatient population

	volunteers	**Study Critique**: • **Strength**: head-to-head treatment comparisons; primary endpoints achieved statistical significance; evaluated objective and subjective sleep parameters • **Weakness**: lack placebo controlled condition; small sample size

Table 3: Low Dose Zolpidem SL for Middle-of-the-Night (MOTN) Awakenings

<table>
<tr><th>Trial/ Objective/Funding</th><th>Study Design/Inclusion/Exclusion/Endpoints</th><th>Results and Conclusions</th></tr>
<tr>
<td>Roth et al. 2008[5]

Objective: To evaluate the efficacy and safety of low-dose, sublingual zolpidem tartrate when taken during a scheduled MOTN awakening in subjects with insomnia characterized by difficulty returning to sleep.

Study was funded by Transcept Pharm. Inc.</td>
<td>Design: R, DB, PC, 3-way cross-over study (conducted in 5 US sleep laboratories)

Screening Periods
• Medical and psychiatric history, physical examination with oral cavity examination, 12-lead ECG, and clinical lab exam (hematology, chemistry, and urinalysis).
• 2 nights of PSG screening to confirm MOTN (mean LPS after the scheduled awakening (LPS_{MOTN}) ≥ 20 minutes across the 2 nights, and a LPS_{MOTN} ≥ 15 minutes on either night

Inclusion:
• Adults aged 18-64 with DSM-IV criteria of insomnia with at least 4 weeks of prolonged MOTN awakenings characterized by at least 3 awakenings per week with a fall back to sleep time ≥ 30 minutes per awakening;
• Screen Sleep Diary completed each morning following awakening and at least 7 out of 10 days must be completed;
• Sleep Diary showed prolonged MOTN awakenings on ≥ 3 nights with mean latency to fall back to sleep ≥ 30 minutes post-awakening;
• Stable bedtime (sleep time: 10 pm-midnight, wake time: 5-8 am);
• Mean LPS_{MOTN} ≥ 20 minutes across 2 nights and a LPS_{MOTN} ≥ 15 minutes on either night confirmed by 2-night PSG single-blind placebo screening which included a 30 minutes scheduled (4 hours after initial light out) awakening

Exclusion:
• Night work or rotating shifts < 6 months prior or anticipated travel requiring crossing more than 3 time zones during course of the study;
• Use of CNS medications or drugs that induce/inhibit hepatic metabolism of zolpidem;
• History of RLS sleep apnea, or narcolepsy; AHI ≥ 10/hour or PLMAI ≥ 10/hour; smoking > 10 cigarettes/day; oral injuries, procedures, or surgery ≤ 60 days prior; known hypersensitivity to</td>
<td>Baseline Patient Characteristics: 203 non-elderly subjects identified, 83 were enrolled, and 82 subjects [24 m; 58 f; mean age 45.9 year (19-64)] were randomized; 80 subjects completed the study. Two subjects discontinued participation due to withdrawal of consent (1) and family emergency (1).
• MOTN awakenings were documented using a 10-day screening sleep diary and confirmed by a 2-night PSG screening of the patients enrolled, two-thirds of subjects experienced ≥ 2 MOTN awakenings per night, and on average, ≥ 60 minutes total wake time after MOTN awakening. (mean LSO_{MOTN} = 75.6 min)

Efficacy*: Mean Primary* and Secondary^ Sleep Parameters
<table>
<tr><th>Parameters</th><th></th><th>Placebo</th><th>Zolpidem 1.75 mg</th><th>Zolpidem 3.5 mg</th></tr>
<tr><td rowspan="4">Mean PSG Parameters (objective)</td><td>LPS_{MOTN} (min)*</td><td>28.12</td><td>16.89 (p<0.001)[a]</td><td>9.69 (p<0.001)[a,b]</td></tr>
<tr><td>TST_{MOTN} (min)^</td><td>183.12</td><td>197.8 (p<0.001)[a]</td><td>208.99 (p<0.001)[a] (p=0.005)[b]</td></tr>
<tr><td>NAW_{MOTN}</td><td>4.13</td><td>3.7</td><td>3.71</td></tr>
<tr><td>$WASO_{MOTN}$ (min)</td><td>15.71</td><td>15.81</td><td>15.06</td></tr>
<tr><td rowspan="2">Mean Patient-Reported Parameters (subjective)</td><td>SOL_{MOTN} (min) ^</td><td>40.43</td><td>28.58 (p<0.001)[a]</td><td>25.23 (p<0.001)[a]</td></tr>
<tr><td>sTST(min) ^</td><td>148.61</td><td>162.36 (p<0.011)[a]</td><td>172.51 (p<0.001)[a]</td></tr>
</table>
* Efficacy analyses were conducted on the modified intent to treat (mITT) population
a. p-values refer to active treatment and placebo
b. p-values refer to zolpidem 1.75 mg and 3.5 mg

Qualitative Rating of Sleep: Zolpidem SL 3.5 mg produced the greatest improvement in Sleep Quality compared to both placebo (p<0.001) and modest improvement to zolpidem SL 1.75 mg dose (p=0.018). Zolpidem SL 1.75 mg did not obtain a significant difference in Sleep Quality compared to placebo. Ratings for Level of Refreshed Sleep and Ability to Function were significantly improved after zolpidem SL 3.5 mg (p<0.001 and p=0.009, respectively), and zolpidem SL 1.75 mg (p=0.017 and p<0.024 respectively) compared to placebo.

Next-Morning Residual Effects: Mean DSST and VAS sedation ratings did not differ from placebo.

Safety: No serious AEs occurred and no subjects discontinued the study due to an AE. A total of 14 subjects reported at least 1 AE during the study (3.5 mg = 4; 1.75 mg= 3; placebo = 7). All AEs were mild in severity and transient. A total of 5 AEs were considered treatment related (3.5 mg (glossodynia) = 1; placebo = 4). No adverse effects on the oral mucosa were reported after treatment of low dose sublingual zolpidem.

Results:
• Sublingual zolpidem produced a significant dose-related response compared to placebo for the primary efficacy endpoint LPS after MOTN awakening (p<0.001) for both the 3.5 mg and 1.75 mg compared to placebo.
• Subject-reported SOL was significantly shorter than placebo (p<0.001)
• Mean TST_{MOTN} values were significantly increased in both active treatments compared to placebo (p<0.001)
• Subject reported estimates of $sTST_{MOTN}$ were significantly longer with the two sublingual formulations compared to placebo (3.5 mg p<0.001 and 1.75 mg p<0.001)
• $WASO_{MOTN}$ and NAW_{MOTN} did not reach significance for both sublingual doses compared to placebo
• Zolpidem SL 3.5 mg produced greatest improvements in Sleep Quality compared to placebo (p<0.001) while</td>
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	zolpidem; participation in clinical research trial within 60 days; history of positive test for HIV, HIBsAG, or anti-HCV; history of drug abuse, excessive alcohol consumption (average > 4 drinks/day) or a positive alcohol breathalyzer test or urine drug screen; pregnant or breastfeeding women **Treatment**: Three 2-night periods in sleep laboratory with placebo, zolpidem SL 1.75 mg, or zolpidem SL 3.5 mg. • Administered within 5 minutes after scheduled MOTN awakening • Subjects were awakened 4 hours after initial lights-out, regardless of sleep stage. Subjects were kept awake for 30 minutes following scheduled awakening before returning to bed for an additional 4 hours of sleep. Each treatment period was separated by 5-12 days washout period. **Assessment**: Efficacy and safety were evaluated using PSG measurements, sleep questionnaires, and residual sedation tests • **Primary Endpoint**: LPS_{MOTN} (zolpidem 3.5 mg and placebo) • **Secondary Endpoints**: Zolpidem 3.5 mg and placebo for the following: objective TST_{MOTN} (principal secondary endpoint), SE_{MOTN}, Rating of sleep quality, subjective SOL_{MOTN}, $sTST_{MOTN}$, and LPS_{MOTN} for zolpidem 1.75 mg and placebo • **Subject Ratings**: Subjects completed a Morning Sleep Questionnaire 30 minutes post PSG termination and VAS was conducted to determine subjects' self-ratings of sedative effects. • **Residual Effect Assessment**: DSST	zolpidem SL 1.75 mg had a relative improvement compared to placebo (p=0.018) • No objective or subjective next day residual sedative effects following awakening in either gender at 4.5 hours after dosing, compared with placebo as measured by DSST and VAS. • Subjective findings of level of Refreshed Sleep, Ability to Function the next morning was significantly improved after both doses of sublingual zolpidem compared to placebo. **Conclusions:** The PSG study utilizing low dose sublingual zolpidem 3.5 mg and 1.75 mg was safe and effective in managing insomnia characterized by difficulty returning to sleep following MOTN awakenings. Both doses of Intermezzo resulted in statistically significant decreases in LPS_{MOTN} and improvement in TST_{MOTN} when compared to placebo. Significant residual sedation was absent for both sublingual doses. **Quality Assessment:** (Good) although may not be generalized to VA population **Study Critique**: • **Strength**: R, DB, PC study with subjective (patient) and objective (PSG) measures; obtained statistical significance with both primary and secondary outcomes; no next-morning residual effects (as long as patient has ≥ 4 hours of sleep remaining); • **Weakness**: no long term efficacy and safety data; no spontaneous awakenings in a naturalistic outpatient setting ("real world" conditions); 3 authors received research support from Transcept; 4 of the 5 members of Intermezzo Study Group were employees of Transcept.

ACRONYMS

AE = adverse event; AHI = apnea-hypopnea index; CFFT = critical flicker fusion test; DSST = digit symbol substitution test); LPS = latency to persistent sleep; LPS_{MOTN} = latency to persistent sleep following MOTN awakening; LSEQ = leeds sleep evaluation questionnaire; LSO = latency to sleep onset; MCRT = multiple choice reaction time; MOTN = middle-of-the-night; NAW = number of awakenings; PLMAI = periodic limb arousal index; PSG = polysomnography; R, DB, PC = randomized, double blind, placebo controlled; REM = time spent in rapid eye movement sleep; RSL = REM sleep latency; SE = sleep efficiency; SE_{MOTN} = sleep efficiency following MOTN awakening; SEI= sleep efficiency index; SOL = sleep onset latency; SOL_{MOTN} = sleep onset latency following MOTN awakening; ST1 = time spent in stage 1; ST1L/LST1 = latency to stage 1; ST2 = time spent in stage 2; ST3 = time spent in stage 3; ST4 = time spent in stage 4; sTST = subjective total sleep time; $sTST_{MOTN}$ = subjective total sleep time following MOTN awakening; SWS = time spent in slow wave sleep; TST = total sleep time; TST_{MOTN} = total sleep time following MOTN awakening; TTA = total time spent awake; VAS = visual analogue scale; WASO = wake time after sleep onset