

Eszopiclone

(Lunesta® - Sepracor)

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Insomnia, reported to affect 5-35% of the population, may be either difficulty falling asleep, staying asleep, or waking early with daytime consequences. Current treatment options include non-pharmacologic therapy, such as improving sleep hygiene or cognitive behavioral therapy, and pharmacologic therapy, including benzodiazepines, nonbenzodiazepine hypnotics and antidepressants.^{2,3} The characteristics of the ideal hypnotic agent outlined at a New Clinical Drug Evaluation Symposium held in 2001 are: rapid absorption, rapid sleep induction, no significant alteration of sleep architecture, appropriate duration of action such that it lasts long enough but does not affect next day functioning, and that the cause of the insomnia is addressed. The ideal hypnotic should not cause residual daytime drowsiness, memory deficits, or respiratory depression, have no interaction with alcohol, not cause tolerance or physical dependence, and not cause rebound insomnia.⁴

PHARMACOLOGY

Eszopiclone, a nonbenzodiazepine hypnotic, is the S-isomer of zopiclone, a hypnotic available in countries other than the U.S. The nonbenzodiazepine hypnotics are chemically unrelated to benzodiazepines, barbiturates, or other drugs with known hypnotic activity; however, they act similar to the benzodiazepines by interacting with the gamma-aminobutyric acid-benzodiazepine (GABA-BZ) receptor complex, specifically the alpha subunit. Subunit modulation of the GABA-BZ receptor chloride channel macromolecular complex is hypothesized to be responsible for some of the pharmacological effects of benzodiazepines, such as sedation, anxiolytic, muscle relaxant, and anticonvulsive effects in animals. The nonbenzodiazepine hypnotics appear to be selective to the α_1 -receptor whereas the benzodiazepines are not selective.^{1,4,5}

PHARMACOKINETICS

Eszopiclone reaches maximum concentration in one hour but is delayed by approximately one hour following a high fat meal. Eszopiclone is metabolized by the cytochrome P450 enzyme system, specifically isoenzymes CYP3A4 and CYP2E1. The elimination half life is six hours, and is increased to approximately 9 hours in patients greater than 65 years of age. The pharmacokinetics of eszopiclone are not significantly altered in patients with renal impairment or mild to moderate hepatic impairment; in patients with severe hepatic impairment the dose should be reduced and should not exceed 2 mg.¹

Summary

Indications. Eszopiclone is indicated for the treatment of insomnia.¹

Monitoring parameters. Sleep latency, duration of sleep and quality of sleep; daytime sleepiness, confusion, withdrawal symptoms, need for dose increases with extended therapy and liver function tests in patients with pre-existing hepatic impairment should be assessed.

Dose. The recommended starting dose of eszopiclone is 2-3 mg immediately before bedtime. For elderly patients with sleep initiation problems, patients with severe hepatic impairment and patients taking potent CYP3A4 inhibitors, the recommended dose is 1 mg. The recommended dose for elderly patients with sleep maintenance problems is 2 mg.

Pregnancy. Category C

Breast Feeding. It is not known if eszopiclone is excreted in breast milk.

Pediatrics. Safety and efficacy in children less than 18 years has not been established.

Geriatrics. Elderly patients may have unusual sensitivity to eszopiclone or impaired motor/cognitive function. See dose modifications in dose section above.

Renal Insufficiency. No dose adjustment is necessary.

Hepatic Insufficiency. Eszopiclone dose should not exceed 2 mg in patients with severe hepatic impairment.

Cost. The average wholesale price (AWP) is \$3.7047 per tablet for 1 mg, 2 mg, and 3 mg tablets.



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CLINICAL TRIALS

The studies used both objective and subjective assessments to evaluate the efficacy of eszopiclone. The objective assessments included polysomnography (PSG) data, including latency to persistent sleep (LPS) defined as the time from lights out to the first 10 minutes of sleep; wake time after persistent sleep onset (WASO); total sleep time (TST) and number of awakenings (NAW). Subjective assessments often were also LPS, WASO, NAW, and TST but as assessed by the patient; additionally, sleep quality and quality of life were also reported by the patient.

TABLE 1. ESZOPICLONE STUDIES

Study	Intervention	LPS (min)	SE (%)	WASO (min)	TST (min)	NAW
Zammit ¹⁰	ESZ 2 mg (n=104)	15 [†]	88.1 ⁺	37.1		6.5
Mean age: 39.8 yr	ESZ 3 mg (n=105)	13.1 [†]	90.1 [†]	33.8 ⁺		5.7
Caucasian: 66.2%	PL (n=99)	29	85.7	44.1		6
Female: 64.6%	44 nights continuously					
Krystal ⁹	ESZ 3 mg (n=595)	30 ^{***}		21	382.5 ^{***}	1.6 ^{***}
Mean age: 44 yr	PL (n=196)	45		30	345	2
Caucasian: 79%	6 months			(p=0.0032)		
Female: 63%						

LPS=latency to persistent sleep; SE=sleep efficiency; WASO=wake time after sleep onset; TST=total sleep time; NAW=number of awakenings/night; ESZ=eszopiclone; PL=Placebo; ***p<0.0001; †p≤ 0.001 vs PL; +p<0.01 vs PL; sleep efficiency (ratio of TST: total time in bed of 8 hr x 100)

Three studies with eszopiclone have been published.⁸⁻¹⁰ The first two^{9, 10} studies were randomized, double-blind, placebo controlled in patients who met the DSM-IV criteria for primary insomnia. The inclusion criteria were similar in that patients had to have total sleep time of less than approximately 6.5 hours per night and needed more than 30 minutes to fall asleep. The baseline BMI and the number of females were significantly higher (p<0.05) in the treatment groups compared to placebo; however, these variables did not change the conclusions of the study when incorporated as covariates in the efficacy analysis model. The results of the studies are summarized in Table 1.

In the study by Zammit et al., eszopiclone increased slightly but significantly the time in stage two of sleep (219 min, 244 min, 252 min for placebo, 2 mg, 3 mg, respectively; p<0.05 for both doses of eszopiclone vs placebo) but the amount of time in the other stages of sleep was not significantly affected.¹⁰

The endpoints assessed in the six-month study with eszopiclone were patient assessments. The primary endpoint was the average sleep latency over the last three months of the first six months of the study and the secondary endpoint was total sleep time over the same time period. These data were not presented or discussed. The authors stated that seven other time points (week one, and monthly values for the six months) and nine different endpoints were analyzed because they were more informative. Data reported in the following table for this study are data from month six.⁹

The third published study evaluated the safety and efficacy of eszopiclone in transient insomnia using a “first-night effect” model.⁸ The study was a prospective, multi-center, randomized, double-blind, placebo-controlled, parallel-group sleep laboratory study. Study participants were normal, healthy adults with normal sleep habits, defined as bedtime between 21:00 and 24:00, sleep onset in less than 30 minutes, sleep lasting from 6.5-10 hours and no report of daytime functioning problems due to sleep. The primary endpoint was objective LPS. Other assessments include PSG measured WASO, sleep efficiency, NAW, sleep architecture, as well as patient reported LPS, TST, NAW, WASO, quality of sleep, and depth of sleep. Study medication was administered at doses of 1, 2, 3 and 3.5 mg. Latency to persistent sleep was significantly shorter with eszopiclone compared to placebo for all doses (p<0.0001) except 1 mg (p=0.06). Wake time after sleep onset was also significantly less with eszopiclone

compared with placebo (p≤0.05). The reduction in NAW was significant with eszopiclone 3 mg and 3.5 mg but not with 1 and 2 mg. Sleep efficiency was also improved with eszopiclone (p≤0.02). The subjective assessments were similar to the objective measures in most of the assessments; the few exceptions were that in some cases when there was a difference by dose in the objective measures, there was not a difference in the subjective measures and vice versa. There were no significant differences in time spent in the various sleep stages between placebo and all doses of eszopiclone except 3.5 mg.

The results of a double-blind, placebo controlled study with eszopiclone in 264 patients age 65-85 years with primary insomnia are available in abstract only. Fourteen nights of eszopiclone 2 mg was compared with placebo. Both objective and subjective assessments were done similar to previously discussed studies. Quality of life was assessed using the Insomnia Severity Index (ISI) and SF-36 questionnaires. Objective assessments of LPS, WASO, sleep efficiency, NAW and subjective assessments of LPS, WASO, TST and NAW were improved with eszopiclone. The number of naps and the duration of naps by the subjects who napped were reduced. The ISI and SF-36 physical function and vitality domains improved with eszopiclone.¹¹

A second study evaluated the safety and efficacy of eszopiclone 2 mg in 64-85 year-old patients with chronic primary insomnia. One hundred fifty-nine patients were randomized to two weeks of either placebo or eszopiclone. Sleep latency was significantly improved (p<0.01) as was WASO (p<0.05), TST (p<0.001), sleep quality (p<0.001), sleep depth (p<0.002), daytime alertness (p<0.05), sense of well-being (p<0.05) and number of naps (p<0.05) and cumulative nap time (p<0.01). Headache was the most common adverse reaction, reported by 15% in both groups.¹²

The data from the 6-month open-label extension phase of the Krystal study are available in abstract form at this time. Four hundred seventy-one patients (111 placebo, 360 eszopiclone) entered the extension phase. Two hundred ninety-six patients received eszopiclone 3 mg for 12 months. The eszopiclone was reported to be well tolerated with no evidence of tolerance and no significant adverse events reported upon discontinuation of study medication.¹³

TABLE 2. DRUG INTERACTIONS^{1,7}

Interacting Drug	Effect
Ethanol	Additive effect on psychomotor performance
Imipramine	Clinical results with zopiclone variable-may have additive hypnotic effects
Chlorpromazine	Enhanced effects of zopiclone although no noted change in pharmacokinetic parameters; dose reduction may be necessary
Olanzapine	DSST scores decreased
CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin, nefazodone, troleandomycin, ritonavir, nelfinavir)	AUC increased, C _{max} and t _{1/2} increased
CYP3A4 inducers (e.g. rifampin, phenobarbital, phenytoin, carbamazepine)	Exposure of racemic zopiclone was reduced 80%, would expect similar results with eszopiclone

DSST=digit symbol substitution test

WARNINGS AND PRECAUTIONS

Signs and symptoms of withdrawal have been reported with rapid dose reduction or discontinuation of eszopiclone.¹ Eszopiclone should be taken just before going to bed and patients should be aware that there is the potential for a reduction in motor coordination and mental alertness the day after taking the medication. The dose of eszopiclone should be reduced in patients taking potent CYP3A4 inhibitors (see drug interactions in Table 2). Eszopiclone is pregnancy category C, which is defined as the risk of harm to the fetus cannot be ruled out; human studies are lacking, and animal studies are either positive for fetal risk or are lacking. However, potential benefits may justify the potential risks.

There is one post-marketing commitment for eszopiclone to be studied in pediatric patients aged 3 to 17 years for the treatment of insomnia.⁶

ADVERSE EVENTS

Adverse events specifically evaluated in the nonbenzodiazepine hypnotic drug class include residual daytime sedation, tolerance and discontinuation or withdrawal syndrome.

Residual daytime sedation

The tools used to assess for residual daytime sedation were not consistent across the studies but may include the digital symbol substitution test (DSST), morning, evening and weekly questionnaires, and visual analog scales (VAS).

The DSST requires patients to recognize symbols and record the associated digit for 90 seconds with the completed number of items being the patient's score.⁸ The 100-mm VAS used zero for being very sleepy and 100 for being not sleepy at all. The weekly questionnaires required the patients to estimate the average of the past week of their daytime ability to function from poor to excellent and daytime alertness from very sleepy to wide awake and alert, both on a scale from 0-10.⁹

The DSST was not reduced after one night of eszopiclone⁸ and was not different than placebo after six weeks of eszopiclone.¹⁰ Other assessments in those studies were either improved (VAS)⁸ or were not significantly different than placebo (questionnaires).¹⁰ In the six-month study by Krystal, daytime ability to function improved and was significantly better with eszopiclone (7 at 6 months) than with placebo (6.3) (p<0.0001). Daytime alertness improved with eszopiclone (6.8 at 6 months) compared with placebo (6) (p<0.0001).⁹

Rebound insomnia/withdrawal syndrome

Rebound insomnia was generally described as a worsening of symptoms compared to baseline and was assessed with single-blind placebo following the double-blind phase of the study. A patient was considered to experience withdrawal if there was a report of "new" events (new or worsening of existing adverse events) since treatment ceased.

There was no difference in reports of withdrawal symptoms or changes in sleep parameters in two eszopiclone studies.^{9,10} There was one report of anxiety with eszopiclone in the six-month eszopiclone study.⁹

Tolerance

Tolerance was typically assessed by a comparison of the efficacy parameters at the end of the study with those noted early in the study or throughout the study.

There was no evidence of tolerance, as measured by LPS, sleep efficiency and WASO on nights 1, 15, and 29.¹⁰ Pharmacologic tolerance was not noted in the study as demonstrated by the improvement in the sleep parameters noted at month one maintained throughout the six months.⁹

Other adverse events

Three patients in the six-week eszopiclone study discontinued therapy due to eszopiclone; in the six-month study, significantly more patients in the eszopiclone group (12.8%) discontinued

TABLE 3. HYPNOTIC PRODUCTS IN DEVELOPMENT²²

Generic name (Manufacturer)	Mechanism of action	Phase
Gaboxadol (Merck)	Direct-acting GABA _A -receptor agonist	Phase 3
Indiplon (Neurocrine Biosciences/Pfizer)	GABA _A -receptor agonist (immediate release and modified release)	Phase 3
Ramelteon (Takeda)	Selective melatonin (ML-1)-receptor agonist	Phase 3
Zolpidem (Sanofi-Aventis)	Controlled-release formulation of zolpidem	Approvable

therapy due to an adverse event compared to placebo (7.1%, $p < 0.05$).^{9, 10}

In the 6-week study, the most common adverse event possibly related to therapy was unpleasant taste (placebo 3%, eszopiclone 2 mg 16.3%, eszopiclone 3 mg 33.3%). Other adverse events reported that may have been treatment-related included abnormal dreams, nervousness, back pain, dizziness, dry mouth, headache, and somnolence.¹⁰

Adverse event rates in the six-month eszopiclone study were 81.1% for the eszopiclone group compared with 70.3% in the placebo group. The most common adverse events were unpleasant taste (eszopiclone 26.1%, placebo 5.6%), headache (19.6%, 19%), infection (15.9%, 6.7%), pain (11.3%, 6.2%), nausea (11.3%, 5.6%), and pharyngitis (9.9%, 5.1%). Most adverse events were mild to moderate in severity. Discontinuation of therapy due to unpleasant taste occurred in 1.7% of eszopiclone patients compared to 0.5% of patients receiving placebo. Serious adverse events were reported in 2.9% of the eszopiclone group and 1% of the placebo group; rates of discontinuation due to serious adverse events were also low at 0.35% with eszopiclone and 0.5% with placebo.⁹

PRODUCT AVAILABILITY/COST/DOSE

Eszopiclone is available as 1 mg, 2 mg, and 3 mg film-coated tablets. The average wholesale price (AWP), \$3.7047, is the same for all three strengths. The recommended initial dose is 2-3 mg immediately before bedtime. For elderly patients with a sleep initiation problem, patients with severe hepatic impairment and patients taking potent CYP3A4 inhibitors, the recommended dose is 1 mg. For elderly patients with a sleep maintenance problem, the recommended dose is 2 mg.

THERAPEUTIC PERSPECTIVE

There are no studies published that were designed to compare the nonbenzodiazepine hypnotic medications head to head. Zolpidem, zaleplon and eszopiclone have all been shown to improve sleep parameters compared to placebo in studies of differing duration. Zaleplon 5 to 20 mg reduces sleep latency; however, likely due to its short half-life zaleplon does not really affect total sleep time.¹⁴ Zolpidem 10-20 mg has also been shown to reduce sleep latency as well as total sleep time.^{15, 16}

The pipeline of new medications being evaluated for use in the treatment of insomnia has three new medications and an extended release formulation of zolpidem. The new products with the respective manufacturer, mechanism of action, and phase of the approval process are summarized in Table 3.

CONCLUSIONS

Eszopiclone, the only nonbenzodiazepine hypnotic that has been studied in a rigorous manner for up to six months, has led to improved objective and subjective assessments with little evidence suggesting that tolerance to eszopiclone developed, or that eszopiclone caused rebound insomnia/withdrawal, next day sedation and adverse reactions. There are no studies designed as head to head comparisons of the different nonbenzodiazepine hypnotics. While there are some differences in the pharmacokinetic profiles of the nonbenzodiazepine hypnotics, specifically the elimination half-life and the change in the AUC in the elderly, which may be indications to select a specific product for a given patient, at the population level these differences may not be clinically significant. Within the next six-18 months, several changes will likely occur affecting the products available for insomnia, given the drugs in development as well as the patent on Ambien[®] due to expire in 2006. ●

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