Eszopiclone (Lunesta™): A New Non-benzodiazepine Sedative–Hypnotic

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INTRODUCTION

Insomnia is a condition that affects nearly everyone at some point in life. Up to 40% of American adults have intermittent insomnia, and 10% to 15% have a chronic sleep problem.1 The main presentation of insomnia is difficulty with either falling asleep or maintaining sleep throughout the night. Complaints of insomnia tend to increase with age. Elderly people report trouble falling asleep, sleeping less at night, waking more often during the night, waking up earlier than they would like, and feeling tired during the day. Younger adults tend to complain more of difficulty falling asleep.2

Insomnia can lead to myriad problems, including next day-drowsiness, decreased performance at work or school, attention and memory problems, depression, and even car accidents. The proper diagnosis and treatment of insomnia are necessary to improve patients’ quality of life; however, insomnia is usually the result of another medical or psychiatric condition. The clinician should rule out all possible causes of insomnia and should address the underlying conditions rather than simply treat the patient with a sedative–hypnotic. Nonpharmacological options, such as sleep-behavior modifications, can also be effective.3

However, sedative–hypnotic agents can play an important role in the treatment of insomnia. These medications reduce the time it takes a person to fall asleep, called the “latency to persistent sleep” (LPS), as well as increase the total sleep time. Until now, sedative–hypnotics were indicated only for the short term, which made them ideal for use while addressing the cause of the patient’s insomnia. Eszopiclone (Lunesta™, Sepracor) is the first sedative–hypnotic drug approved by the Food and Drug Administration (FDA) for the long-term treatment of insomnia. In clinical trials of up to 12 months, no decrease in effectiveness has been observed.4

CHEMICAL AND PHYSICAL PROPERTIES

Eszopiclone, a non-benzodiazepine hypnotic agent, is a pyrrolopyrazine derivative of the cyclopyrrolone class. It is the (S)-configuration isomer of zopiclone (Imovane™, Aventis), a hypnotic agent that has been available in Europe since 1987. Eszopiclone is a white to light-yellow crystalline solid. According to the manufacturer, it is very slightly soluble in water, slightly soluble in ethanol, and soluble in phosphate buffer.3 It is available as film-coated tablets in dosages of 1, 2, and 3 mg.

MECHANISM OF ACTION

Although the exact mechanism of action of eszopiclone is unknown, its hypnotic effect is thought to result from its interaction with the gamma-aminobutyric acid (GABA) receptor at receptors close to or allosterically coupled to the benzodiazepine receptor.3

PHARMACOKINETICS

Absorption and Distribution

Eszopiclone is rapidly absorbed after oral administration. According to the manufacturer, the peak plasma (Cmax) and time to maximum concentrations (Tmax) are achieved within one hour after oral administration. The plasma protein-binding property for eszopiclone is weak, with only 52% to 59% being protein-bound. As a result of this weak protein binding, drug–drug interactions caused by protein binding should not occur, and none have been reported. Administration of eszopiclone after a high-fat meal results in a reduction of the Cmax by 21% and in a delay of one hour for the Tmax. However, no change in the area-under-the-curve (AUC) concentration has been observed.3

Metabolism and Elimination

Eszopiclone is metabolized by oxidation and demethylation into (S)-zopiclone-N-oxide and (S)-N-desmethylzopiclone. The latter compound retains some potency in binding to GABA receptors, but its potency is substantially lower than that of eszopiclone. The former compound shows no significant binding to the GABA receptor. The cytochrome isoenzymes CYP450 3A4 and CYP450 2E1 are also involved in eszopiclone metabolism, as shown in in vitro studies. Extra monitoring is necessary when eszopiclone is administered with a CYP3A4 inhibitor or inducer. Eszopiclone does not appear to have any CYP450 inhibitory properties. Its half-life is approximately six hours. Less than 10% of the orally administered eszopiclone dose is excreted in the urine as the parent drug.

ADVERSE DRUG EFFECTS

On the basis of two published clinical trials (see “Clinical Efficacy” on page 389), the most commonly reported adverse drug event (ADE) was an unpleasant taste, with an incidence of 17% to 26%, with no dose-dependent relationship. Somnolence was reported.
equally at all doses, with an incidence of 4% to 9%. However, headache was reported with the same frequency as placebo in both trials (9% and 19%).

The incidence of dizziness was greater than 5% in both trials. In the clinical trial by Krystal et al., the dry mouth (6.6%), infection (15.9%), nausea (11.3%), pain (11.3%), and pharyngitis (9.9%) were all reported at a higher frequency with the study drug than with placebo.

No clinically significant laboratory, cardiovascular, or electrocardiographic changes were reported in these studies, and there were no significant withdrawal symptoms upon discontinuation of the drug.

**INDICATIONS**

Eszopiclone is a schedule IV drug indicated for the treatment of insomnia in adults (at least 18 years of age). There are no contraindications to the use of eszopiclone other than a known hypersensitivity to eszopiclone, zopiclone, or any of its components.

**DOSEAGE**

**Adults**

The recommended dose for non-elderly adults is 2 mg at bedtime, to be increased to 3 mg if needed. Zammit et al. compared placebo, eszopiclone 2 mg, and eszopiclone 3 mg in adults younger than 65 years of age. The 2-mg and 3-mg dosages were found to be equally efficacious in reducing sleep latency. The 3-mg strength provided a higher median total sleep time of 406 minutes, whereas 2 mg provided 400 minutes.

In a trial comparing eszopiclone 1, 2, 3, and 3.5 mg with placebo, all doses were found to be equally efficacious in reducing sleep latency; however, total sleep time was slightly increased across the dosage range (see “Clinical Efficacy”). In general, however, treatment should be individualized for each patient.

**Elderly Patients**

A starting dose of 1 mg is recommended for older adults whose primary complaint is difficulty falling asleep. This dose can be increased to 2 mg if needed. If the main complaint is difficulty staying asleep, eszopiclone can be initiated at 2 mg at bedtime.

The AUC concentration was increased by 41% in elderly patients when compared with non-elderly adults. In one clinical trial comparing eszopiclone 1 mg and 2 mg in elderly patients, both dosages were found to be superior to placebo in terms of sleep onset and total sleep time. Both dosages were also well tolerated.

**Hepatically Impaired Patients**

Eszopiclone should be used with caution in patients with severe hepatic impairment; in these patients, systemic exposure increased by 74%. The package insert recommends a starting dose of 1 mg. No dose adjustment appears to be necessary in patients with mild-to-moderate hepatic impairment.

**Patients with Renal Impairment**

No dosage adjustment is indicated for patients with renal impairment, but systemic exposure to the drug increased by 29% to 47% in patients with severe renal impairment. Patients with renal impairment should be closely monitored for side effects or excessive sedation.

**Pregnant and Lactating Patients**

Eszopiclone is categorized as a pregnancy category C drug. No studies have been conducted with eszopiclone in pregnant women or nursing mothers. It is not known whether eszopiclone is excreted in human milk. The potential risks and benefits of using eszopiclone should be considered before it is prescribed during pregnancy or lactation.

**DRUG INTERACTIONS**

Because eszopiclone is metabolized via CYP3A4 and CYP2E1, caution is recommended when a potent CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, clarithromycin, troleandomycin, nefazodone, ritonavir, nelfinavir) is co-administered. A lower dose, such as 1 mg, should be prescribed when eszopiclone is used with any of these drugs.

**CLINICAL EFFICACY**

Krystal et al./Roth et al.

The first part of this two-part study was a six-month double-blind, placebo-controlled trial, the second part being a six-month open-label extension, which was available to all patients who completed the double-blind portion of the study. The patients received either eszopiclone 3 mg or placebo.

To be eligible for enrollment in the study, patients had to:

- be between the ages of 21 and 65 years of age.
- have a diagnosis of primary insomnia, as described in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition.
- report a usual total sleep time of less than 6.5 hours per night and/or a usual sleep latency of more than 30 minutes each night for at least one month prior to screening. (Sleep latency was defined as the time it took a patient to fall asleep.)

Patients were excluded from the study if they:

- met criteria for another DSM-IV Axis I diagnosis or Axis II personality disorder.
- had a history of substance abuse or substance dependence.
- consumed more than two alcoholic beverages per day or more than 14 per week.
- used any psychotropic, hypnotic, or other medication known to affect sleep.
- used over-the-counter products containing caffeine or herbal supplements, including melatonin and St. John’s Wort.

Of the 1,194 patients screened for the trial, 788 were randomly assigned to receive either eszopiclone 3 mg (n = 593) or placebo (n = 195). Baseline demographics were similar in both treatment arms, but the eszopiclone patients had a statistically significant higher mean body mass index and weight (mean, 29.5 kg/m²) than the placebo patients (mean, 27.8 kg/m²). Discontinuation rates were similar in the eszopiclone treatment arm (39.5%) and in the placebo arm (43.4%).

The primary endpoint was originally defined as the average sleep latency over the last three months of the double-blind portion of the study, and the key secondary endpoint was the average total sleep time during the same period. The patients called in to an interactive voice response system once weekly to report their sleeping patterns. At the end of the six-month study, the investigators decided it would be best to publish the
information for seven different time points (at the first week and at months one to six) rather than for only the three original time points.

Baseline characteristics for sleep latency were higher with placebo than with eszopiclone. The median sleep latency was 60 minutes with eszopiclone and 75 minutes with placebo. However, the investigators reported that this difference was not statically significant ($P = .6317$). By the first week, the median sleep latency had decreased to 30 minutes with eszopiclone and to 60 minutes with placebo ($P < .0001$). The median sleep latency for the eszopiclone treatment arm remained at or close to 30 minutes for the remainder of the six-month study.

For the placebo treatment arm, the median sleep time decreased to 45 minutes by the third month and remained at that level for the remainder of the study. By the sixth month, the difference in median sleep latency times was 15 minutes between placebo and eszopiclone. This 15-minute difference was found to be statistically significant ($P < .0001$).

For the key secondary endpoint of sleep duration, both treatment groups had a baseline median total sleep time of 300 minutes. By the first week, the median total sleep time was 330 minutes for the placebo patients and 375 minutes for the eszopiclone patients. By the sixth month, the median total sleep time was 339.3 minutes with placebo and 382.5 minutes with eszopiclone ($P < .0001$).

The most commonly reported AEs in the patients receiving eszopiclone, in contrast to those receiving placebo, were dizziness, dry mouth, infection, nausea, pain, and pharyngitis. Notable differences in effects were the reports of an unpleasant taste (5.6% with placebo vs. 26.1% with eszopiclone) and infection (6.7% with placebo vs. 15.9% with eszopiclone).

Following discontinuation of the drug, no significant withdrawal effects were observed; there was only one report of anxiety after eszopiclone was stopped. There were no reports of seizures, hallucinations, or perceptual-disturbance events. The authors did not mention the method of discontinuation used in the study.

The investigators concluded that the nightly use of eszopiclone 3 mg resulted in improved sleep onset, sleep maintenance, sleep quality, and next-day functioning, compared with placebo ($P < .0001$). This study also showed no tolerance effect upon discontinuation.

The same results were seen in the six-month open-label extension phase of this trial. Patients previously treated with placebo reported rapid and significant improvements in sleep and daytime functioning ($P < .05$). Patients who took eszopiclone for 12 months showed no evidence of tolerance.

**Rosenberg et al.**

Rosenberg and colleagues conducted a randomized, double-blind, placebo-controlled study to assess the efficacy and safety of a one-time dose of eszopiclone using the “first-night effect” model of transient insomnia. The first-night effect refers to the insomnia that commonly occurs when someone is assessed in a sleep laboratory.

A total of 436 adults aged 25 to 50 years were randomly assigned to receive either placebo or eszopiclone 1, 2, 3, or 3.5 mg. Participants had to have a body mass index between 16 and 30 kg/m², no history of insomnia, and a report of normal sleep patterns.

Participants were excluded from the study if they:
- had previously slept in a sleep laboratory.
- had symptoms of a primary sleep disorder.
- had a known hypersensitivity to zopiclone or other hypnotic agents.
- had any unstable medical conditions or a history of psychiatric problems.

Participants were instructed to avoid taking any over-the-counter analgesics within seven days of the study or any other medication within 14 days, and they were required not to have used tobacco or nicotine products within the previous three months. Caffeine intake was limited to 180 mg daily, and no caffeine or alcohol was allowed after 2 p.m. on the day of the study.

The primary endpoint was latency to persistent sleep (LPS), as measured objectively by polysomnography. LPS was defined as the time from “lights out” (bedtime) to the beginning of 10 uninterrupted minutes of sleep. Objective secondary measures included:
- wake time (the time spent awake during undesired awakenings) after initial sleep onset.
- sleep efficiency.
- the number of awakenings lasting at least one minute.
- sleep architecture (the stages and cycles of sleep).

All of these measures were obtained via polysomnography. Subjective measures were also obtained from the patients, including quality of sleep and depth of sleep. Safety was assessed via clinical laboratory tests, electrocardiograms, vital signs, physical and neurological examinations, and the occurrence of ADEs.

A total of 436 patients were randomly selected to receive either placebo or eszopiclone 1, 2, 3, or 3.5 mg. The baseline characteristics were similar for all five groups. Subjects who received 2, 3, and 3.5 mg had a statistically significant shorter LPS compared with those receiving placebo ($P < .0001$). For those taking eszopiclone 1 mg, the LPS was reduced but did not differ significantly from that in the placebo group ($P = .06$).

The wake time after sleep onset was significantly reduced in all patients taking eszopiclone compared with that in those taking placebo ($P < .05$). The number of awakenings was significantly decreased with eszopiclone 3 and 3.5 mg compared with placebo ($P < .005$). Sleep efficiency, or total sleep time, significantly increased in all eszopiclone patients compared with placebo patients ($P < .02$).

Self-reported total sleep time increased significantly in the patients taking 2, 3, and 3.5 mg compared with the placebo patients ($P < .01$). More patients treated with eszopiclone reported deep or very deep sleep compared with the placebo subjects ($P < .01$). All of the study drug groups, except for those taking 1 mg, reported good or excellent quality of sleep compared with the placebo group ($P < .0001$). However, more patients in the 3- and 3.5-mg treatment groups reported morning drowsiness compared with those in the placebo group ($P < .05$).

Sleep architecture did not change significantly in any of the treatment groups.
except with eszopiclone 3.5 mg, when compared with placebo. The 3.5-mg group experienced a statistically significant decrease in total time spent in non-rapid-eye movement (NREM) stage 1 sleep and rapid-eye movement (REM) sleep, as well as a statistically significant increase in time spent in NREM stage 2 ($P \leq .05$) sleep. Stages 3 and 4, which are the restorative stages of sleep, did not change significantly in any of the treatment groups.

The most commonly reported ADEs with all doses were headache, somnolence, and unpleasant taste. Dizziness was reported more often with the patients who received 3.5 mg of eszopiclone. An unpleasant taste was the only ADE reported with more frequency in the eszopiclone groups (range, 17.0–21.6%) than in the placebo group (7.1%). There were no abnormal laboratory parameters, vital signs, or electrocardiographic changes.

The authors concluded that the doses of 2 and 3 mg were the most effective for treating transient insomnia without affecting sleep structure or causing next-day drowsiness.5

**COST**

The average wholesale price (AWP) of a month’s supply of eszopiclone 1-mg tablets is $111. The price is the same for the 2- and 3-mg tablets. This charge may vary according to acquisition costs in different health care systems.

The other leading hypnotic agent, zolpidem (Ambien™, Sanofi-Synthelabo), is less expensive ($78.90 for a month’s supply of 5-mg tablets and $96.70 for the 10-mg tablets). The AWP of zaleplon (Sonata™, Wyeth) is $74.40 for a month’s supply of 5-mg capsules and $91.50 for the 10-mg capsules.

Further research is needed to compare these drugs and to determine whether the higher cost of eszopiclone is rational. Because all three drugs have a similar mechanism of action, one would not expect much difference in their efficacy.

**CONCLUSION**

The advantages of eszopiclone include its quick onset and proper duration of action, little next-day residual drowsiness, and a low incidence of ADEs. This agent is unique among the sedative–hypnotics, in that the FDA has not limited its use in the short-term treatment of insomnia. However, caution must be used when treating insomnia chronically with an oral medication. True primary insomnia is rare. Insomnia is often the result of another underlying untreated medical condition or psychiatric illness. Physicians and pharmacists should conduct a thorough assessment of a patient’s complaint of insomnia before prescribing any sedative–hypnotics.

**REFERENCES**