



FDA adds Boxed Warning for risk of serious injuries caused by sleepwalking with certain prescription insomnia medicines

### Safety Announcement

**[04-30-2019]** The Food and Drug Administration (FDA) is advising that rare but serious injuries have happened with certain common prescription insomnia medicines because of sleep behaviors, including sleepwalking, sleep driving, and engaging in other activities while not fully awake. These complex sleep behaviors have also resulted in deaths. These behaviors appear to be more common with eszopiclone (Lunesta), zaleplon (Sonata), and zolpidem (Ambien, Ambien CR, Edluar, Intermezzo, Zolpimist) than other prescription medicines used for sleep.

As a result, we are requiring a *Boxed Warning*, our most prominent warning, to be added to the [prescribing information](#) and the patient [Medication Guides](#) for these medicines. We are also requiring a *Contraindication*, our strongest warning, to avoid use in patients who have previously experienced an episode of complex sleep behavior with eszopiclone, zaleplon, and zolpidem.

Serious injuries and death from complex sleep behaviors have occurred in patients with and without a history of such behaviors, even at the lowest recommended doses, and the behaviors can occur after just one dose. These behaviors can occur after taking these medicines with or without alcohol or other central nervous system depressants that may be sedating such as tranquilizers, opioids, and anti-anxiety medicines.

Eszopiclone, zaleplon, and zolpidem are medicines used to treat insomnia in adults who have difficulty falling asleep or staying asleep. They are in a class of medicines called sedative-hypnotics and have been approved and on the market for many years. These insomnia medicines work by slowing activity in the brain to allow sleep. Quality sleep can have a positive impact on physical and mental health.

**Health care professionals** should not prescribe eszopiclone, zaleplon, or zolpidem to patients who have previously experienced complex sleep behaviors after taking any of these medicines. Advise all patients that although rare, the behaviors caused by these medicines have led to serious injuries or death. Tell the patient to discontinue taking these medicines if they experience an episode of complex sleep behavior.

**Patients** should stop taking your insomnia medicine and contact your health care professional right away if you experience a complex sleep behavior where you engage in activities while you are not fully awake or if you do not remember activities you have done while taking the medicine.

We identified 66 cases of complex sleep behaviors occurring with these medicines over the past 26 years that resulted in serious injuries, including death (see Data Summary). This number includes only reports submitted to FDA\* or those found in the medical literature,<sup>1-5</sup> so there may be additional cases about which we are unaware. These cases included accidental overdoses, falls, burns, near drowning, exposure to extreme cold temperatures leading to loss of limb, carbon monoxide poisoning, drowning, hypothermia, motor vehicle collisions with the patient driving, and self-injuries such as gunshot wounds and apparent suicide attempts. Patients usually did not remember these events. The underlying mechanisms by which these insomnia medicines cause complex sleep behaviors are not completely understood.

FDA is also reminding the public that all medicines taken for insomnia can impair driving and activities that require alertness the morning after use. Drowsiness is already listed as a common side effect in the drug labels of all insomnia medicines, along with warnings that patients may still feel drowsy the day after taking these products. Patients who take insomnia medicines can experience decreased mental alertness the morning after use even if they feel fully awake.

We communicated safety information associated with certain insomnia medicines in [January 2013](#) (risk of next-morning impairment with zolpidem), [May 2013](#) (approved lower recommended doses for zolpidem), and [May 2014](#) (risk of next-morning impairment with eszopiclone; lowered recommended dose). We are continuing to monitor the safety of insomnia medicines and will update the public as new information becomes available.

To help FDA better track safety issues with medicines, we urge health care professionals and patients to report side effects involving eszopiclone, zaleplon, and zolpidem or other medicines to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.

\*The cases were reported to the [FDA Adverse Event Reporting System \(FAERS\)](#).

### **Facts about Eszopiclone (Lunesta), Zaleplon (Sonata), and Zolpidem (Ambien, Ambien CR, Edluar, Intermezzo, Zolpimist)**

- Eszopiclone, zaleplon, and zolpidem are prescription sedative-hypnotic medicines used to treat insomnia in adults who have difficulty falling asleep or staying asleep.
- These medicines work by slowing activity in the brain.
- Eszopiclone was approved in December 2004. It is available as an oral tablet under the brand name Lunesta and in generic form.
- Zaleplon was approved in August 1999. It is available as an oral capsule under the brand name Sonata and in generic form.
- Zolpidem was initially approved in December 1992. It is available as an oral tablet under the brand name Ambien and in generic form, an extended-release tablet (Ambien CR and generics), a sublingual tablet taken under the tongue (Edluar), and an oral spray (Zolpimist). Zolpidem is also available under the brand name Intermezzo, a lower dose sublingual tablet that is approved for use as needed for the treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep.

- More common side effects of these insomnia medicines include drowsiness, dizziness, diarrhea, and grogginess or feeling as if you have been drugged.
- Less common serious side effects of these insomnia medicines can include:
  - Getting out of bed while not being fully awake and doing an activity you do not know you are doing or do not later remember doing.
  - Abnormal thoughts and behavior. Symptoms include more outgoing or aggressive behavior than normal, confusion, agitation, hallucinations, worsening of depression, and suicidal thought or actions.
  - Memory loss
  - Anxiety
  - Severe allergic reactions. Symptoms include swelling of the tongue or throat, and trouble breathing.
- In 2018, an estimated 26.6 million zolpidem prescriptions were dispensed from U.S. outpatient retail pharmacies, followed by 2.7 million prescriptions dispensed for eszopiclone and 600,000 zaleplon prescriptions. In the same year and setting, an estimated 5.1 million total patients received a zolpidem prescription, 600,000 total patients received an eszopiclone prescription, and 200,000 total patients received a zaleplon prescription.<sup>6</sup>

### **Additional Information for Patients and Caregivers**

- Eszopiclone, zaleplon, and zolpidem can cause complex sleep behaviors, including sleepwalking, sleep driving, and engaging in other activities while not fully awake. These complex sleep behaviors are rare but have resulted in serious injuries and death.
- These events can occur with just one dose of these medicines as well as after a longer duration of treatment.
- If you experience a complex sleep behavior, stop taking the medicine and contact your prescriber immediately.
- FDA is also reminding the public that all medicines taken for insomnia can impair driving and activities that require alertness the morning after use. Drowsiness is already listed as a common side effect in the prescribing information of all insomnia medicines, along with warnings that patients may still feel drowsy the day after taking these products. Patients who take insomnia medicines can experience impairment of mental alertness the morning after use, even if they feel fully awake.
- Use your insomnia medicine exactly as directed. To lessen the chances of side effects and adverse events, never take more than prescribed and do not take it more often than prescribed.
- Do not take eszopiclone, zaleplon, or zolpidem if you will be unable to remain asleep for the required number of hours after taking the medicine. If you get up too soon after taking the medicine, you may experience drowsiness and problems with memory, alertness, or coordination.
  - If you are taking eszopiclone tablets (Lunesta), zolpidem tablets (Ambien), extended-release tablets (Ambien CR), sublingual tablets (Edluar), or oral spray (Zolpimist), you should plan to go to bed right after taking the medicine and stay in bed for 7 to 8 hours.

- If you are taking zaleplon (Sonata) or zolpidem (Intermezzo), you should take the medicine in bed and remain in bed for at least 4 hours.
- Do not take eszopiclone, zaleplon, and zolpidem with any other sleep medicines, including over-the-counter medicines you can buy without a prescription. Do not drink alcohol before taking these medicines because the combined effects can increase the chances of side effects and adverse events.
- Read the patient [Medication Guide](#) every time you receive a prescription. The Medication Guide will be updated with this new or other important information about your medicine. It explains the important things that you need to know about the medicine. These include the side effects, what the medicine is used for, how to take and store it properly, and other things to watch out for when you are taking the medicine.
- For information on healthy sleep habits, visit the [National Heart, Lung, and Blood Institute for resources, including: Your Guide to Healthy Sleep](#) and [Insomnia: Relaxation techniques and sleeping habits](#).
- We communicated safety information associated with insomnia medicines in [January 2013](#) (risk of next-morning impairment with zolpidem), [May 2013](#) (approved lower recommended doses for zolpidem), and [May 2014](#) (risk of next-morning impairment with eszopiclone; lowered recommended dose).
- To help FDA track safety issues with medicines, report side effects from eszopiclone, zaleplon, zolpidem, or other medicines to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of this page.

### **Additional Information for Health Care Professionals**

- Complex sleep behaviors, in which patients engage in activities while they are not fully awake, resulting in serious injuries and death have been reported with eszopiclone, zaleplon, and zolpidem.
- These events can occur with just one dose of these medicines as well as after a longer duration of treatment.
- Eszopiclone, zaleplon, and zolpidem are contraindicated in patients who report an episode of complex sleep behavior after taking these insomnia medicines.
- Tell patients to discontinue their insomnia medicine if they experience an episode of complex sleep behavior even if it did not result in a serious injury.
- When starting patients on eszopiclone, zaleplon, or zolpidem, follow the dosing recommendations in the prescribing information and start with the lowest possible dose.
- Encourage patients to read the [Medication Guide](#) every time they fill their eszopiclone, zaleplon, or zolpidem prescriptions, and remind them not to combine them with other insomnia medicines, alcohol, or CNS depressants.
- We communicated safety information associated with insomnia medicines in [January 2013](#) (risk of next-morning impairment with zolpidem), [May 2013](#) (approved lower recommended doses for zolpidem), and [May 2014](#) (risk of next-morning impairment with eszopiclone; lowered recommended dose).
- To help FDA track safety issues with medicines, report adverse events involving eszopiclone, zaleplon, zolpidem, or other medicines to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of this page.

## Data Summary

FDA identified 62 cases of complex sleep behaviors that resulted in serious injuries or death after taking insomnia medicines eszopiclone, zaleplon, or zolpidem reported in the [FDA Adverse Event Reporting System \(FAERS\) database](#) between December 16, 1992, and February 27, 2018, and four additional cases reported in the medical literature<sup>1-5</sup> between December 16, 1992, and March 13, 2018. Of the 66 cases, 20 cases were reported as resulting in fatal outcomes. Forty-six cases reported serious non-fatal injuries; these patients usually did not remember experiencing these complex sleep behaviors. The underlying mechanisms by which these insomnia medicines cause complex sleep behaviors are not completely understood.

The cases reported one or more episodes of the sleep behaviors and reported one or more adverse events. The adverse events included falls (n=22) with serious injuries such as intracranial hemorrhages, vertebral fractures, and hip fractures. Other events included self-injuries (n=7), fatal falls (n=6), accidental overdoses (n=5), hypothermia (n=5), suicide attempts (n=5), apparent completed suicides (n=4), fatal motor vehicle collisions (n=4), gunshot wounds (n=3), carbon monoxide poisoning (2), drowning or near drowning (n=2), burns (n=2), and homicide (n=1).

Most of these patients reported using zolpidem (n=61) when they experienced a complex sleep behavior. The remaining patients took eszopiclone (n=3) or zaleplon (n=2). These data are consistent with the higher number of zolpidem prescriptions dispensed compared to eszopiclone and zaleplon.

## Resources

1. Chopra A, Selim B, Silber MH, Krahn L. Para-Suicidal Amnestic Behavior Associated with Chronic Zolpidem Use: Implications for Patient Safety. *Psychosomatics*. 2013;54(5):498-501.
2. Das P, Dutt T. A veteran who is suicidal while sleeping. *Current Psychiatry*. 2017;16(4):43-49.
3. Gibson CE, Caplan JP. Zolpidem-Associated Parasomnia with Serious Self-Injury: A shot in the Dark. *Psychosomatics*. 2011;(52(1):88-91.
4. Liskow B, Pikalov A. Zaleplon overdose associated with sleepwalking and complex behavior. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2004;43(8):927-928.
5. Polasek TM, vidya P, Yolande L. Serious adverse drug reactions to zolpidem: does impaired metabolic clearance and concurrent SSRI/SNRI use increase risk? *Journal of Pharmacy Practice and Research*. 2016;46(2):139-142.
6. IQVIA National Prescription Audit™ (NPA) and Total Patient Tracker™ (TPT) Databases. Year 2018. Data Extracted February 2019.

## Related Information

- [Sleep Disorder \(Sedative-Hypnotic\) Drug Information](#)
- [Insomnia: Relaxation technique and sleeping habits](#)
- [National Heart, Lung, and Blood Institute: Your Guide to Health Sleep](#)

- [The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective](#)
- [Think It Through: Managing the Benefits and Risks of Medicines](#)