



U.S. Food and Drug Administration  
Protecting and Promoting Your Health

## Drug Safety Communications

### **Risk of next-morning impairment after use of insomnia drugs; FDA requires lower recommended doses for certain drugs containing zolpidem (Ambien, Ambien CR, Edluar, and Zolpimist)**

#### **Safety Announcement**

**[1-10-2013]** The U.S. Food and Drug Administration (FDA) is notifying the public of new information about zolpidem, a widely prescribed insomnia drug. FDA recommends that the bedtime dose be lowered because new data show that blood levels in some patients may be high enough the morning after use to impair activities that require alertness, including driving. Today's announcement focuses on zolpidem products approved for bedtime use, which are marketed as generics and under the brand names Ambien, Ambien CR, Edluar, and Zolpimist.

FDA is also reminding the public that all drugs 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 drugs, along with warnings that patients may still feel drowsy the day after taking these products. Patients who take insomnia drugs can experience impairment of mental alertness the morning after use, even if they feel fully awake.

FDA urges health care professionals to caution all patients (men and women) who use these zolpidem products about the risks of next-morning impairment for activities that require complete mental alertness, including driving. For zolpidem products, data show the risk for next-morning impairment is highest for patients taking the extended-release forms of these drugs (Ambien CR and generics). Women appear to be more susceptible to this risk because they eliminate zolpidem from their bodies more slowly than men (see Data Summary below).

Because use of lower doses of zolpidem will result in lower blood levels in the morning, FDA is requiring the manufacturers of Ambien, Ambien CR, Edluar, and Zolpimist to lower the recommended dose. FDA has informed the manufacturers that the recommended dose of zolpidem for women should be lowered from 10 mg to 5 mg for immediate-release products (Ambien, Edluar, and Zolpimist) and from 12.5 mg to 6.25 mg for extended-release products (Ambien CR). FDA also informed the manufacturers that, for men, the labeling should recommend that health care professionals consider prescribing the lower doses—5 mg for immediate-release products and 6.25 mg for extended-release products (see Zolpidem Dosing Recommendations for Adults).

The recommended doses of Intermezzo, a lower dose zolpidem product approved for middle-of-the-night awakenings, are not changing. At the time of Intermezzo's approval in November 2011, the label already recommended a lower dosage for women than for men.

FDA is continuing to evaluate the risk of impaired mental alertness with other insomnia drugs, including over-the-counter (OTC) drugs available without a prescription.

To decrease the potential risk of impairment with all insomnia drugs, health care professionals should prescribe, and patients should take, the lowest dose capable of treating the patient's insomnia. Patients who drive or whose activities require full alertness the morning after use of an insomnia drug should discuss the appropriateness of their medicine with their health care professional (see Insomnia Medicines below).

FDA has prepared a list of [questions and answers](#) to provide an additional overview of this safety issue.

### **Facts about Zolpidem**

- A sedative-hypnotic (sleep) medicine used in adults for the treatment of insomnia
- Marketed as generics and under the brand-names Ambien, Ambien CR, Edluar, Zolpimist, and Intermezzo
- In 2011, about 39 million prescriptions for zolpidem products were dispensed, and about 9 million patients received zolpidem products from U.S. outpatient retail pharmacies, of which 63% of the patients were female. Extended-release zolpidem products (Ambien CR<sup>®</sup> and generics) accounted for 11% (4.4 million prescriptions) of the zolpidem market, immediate-release products accounted for 89% (35 million prescriptions) of the market in Y2011.<sup>1</sup>

### **Additional Information for Patients**

- Patients who take insomnia medicines can experience decreased mental alertness the morning after use, even if they feel fully awake.
- Zolpidem extended-release (Ambien CR and generics) products may not be the right medication choice for patients (men or women) with insomnia who need to drive or perform activities that require full alertness the next morning.
- For women, FDA is requiring the manufacturers of zolpidem-containing products to lower the recommended doses of Ambien and Ambien CR, Edluar, and Zolpimist in the professional drug labels that accompany the medications. FDA is also requiring manufacturers to recommend that health care professionals consider prescribing the lower dose of these drugs in men (see Zolpidem Dosing Recommendations for Adults).

- If you are currently taking the 10 mg or 12.5 mg dose of a zolpidem-containing insomnia medicine, continue taking your prescribed dose as directed until you have contacted your health care professional to ask for instructions on how to safely continue to take your medicine. Each patient and situation is unique, and the appropriate dose should be discussed with your health care professional.
- The lower zolpidem dose will be effective in most women and many men.
- Read the Medication Guide that comes along with your zolpidem prescription for additional information.
- For other insomnia medicines, talk to your health care professional about ways to take the lowest dose that treats your symptoms.
- Take your insomnia medicine exactly as prescribed.
- Over-the-counter (OTC) insomnia medicines that are available without a prescription should not be considered safer than prescription insomnia medicines for next-morning alertness and driving.
- Contact your health care professional if you have any questions or concerns about zolpidem or other insomnia medicines.
- Report side effects from the use of zolpidem or other insomnia medicines to FDA's MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

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

- Immediate-release products: FDA is requiring the manufacturers of certain immediate-release zolpidem products (Ambien, Edluar, and Zolpimist) to lower the recommended dose. FDA has informed manufacturers that:
  - The recommended initial dose for women should be lowered from 10 mg to 5 mg, immediately before bedtime.
  - The drug labeling should recommend that health care professionals consider prescribing a lower dose of 5 mg for men. In many men, the 5 mg dose provides sufficient efficacy.
  - The drug labeling should include a statement that, for both men and women, the 5 mg dose could be increased to 10 mg if needed, but the higher dose is more likely to impair next-morning driving and other activities that require full alertness.
- Extended-release products: FDA is also requiring the manufacturer of extended-release zolpidem (Ambien CR) to lower the recommended dose. FDA has informed the manufacturer that:
  - The recommended initial dose for women should be lowered from 12.5 mg to 6.25 mg, immediately before bedtime.
  - The drug labeling should recommend that health care professionals consider prescribing a lower dose of 6.25 mg in men. In many men, the 6.25 mg dose provides sufficient efficacy.

- The drug labeling should include a statement that, for both men and women, the 6.25 mg dose can be increased to 12.5 mg if needed, but the higher dose is more likely to impair next-morning driving and other activities that require full alertness.
- FDA has informed the manufacturers that the recommended zolpidem doses for women and men should be different because women eliminate zolpidem from their bodies at a slower rate than men.
- For zolpidem and other insomnia drugs, prescribe the lowest dose that treats the patient's symptoms.
- FDA urges health care professionals to caution all patients (men and women) who use these products about the risks of next-morning impairment for activities that require complete mental alertness, including driving.
- Inform patients that impairment from sleep drugs can be present despite feeling fully awake.
- Encourage patients to read the Medication Guide when they receive their zolpidem prescription.
- Report adverse events involving zolpidem or other insomnia drugs to FDA's MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

### **Data Summary**

Driving simulation and laboratory studies recently submitted to FDA indicate that zolpidem blood levels above approximately 50 ng/mL appear capable of impairing driving to a degree that increases the risk of a motor vehicle accident. In pharmacokinetic trials of 10 mg Ambien (or bioequivalent zolpidem products) that included approximately 250 men and 250 women, about 15% of women and 3% of men had zolpidem concentrations that exceeded 50 ng/mL approximately 8 hours post-dosing. Three measurements in women and one in men were  $\geq 90$  ng/mL at about 8 hours after use.

A higher percentage of both men and women experience potentially impairing morning zolpidem levels after use of extended-release zolpidem products (Ambien CR or generic equivalents). In pharmacokinetic trials of zolpidem extended-release 12.5 mg, approximately 33% of women and 25% of men had zolpidem blood concentrations exceeding 50 ng/mL approximately 8 hours post-dosing. About 5% of patients had blood levels  $\geq 100$  ng/mL.

In studies of zolpidem extended-release 6.25 mg, at 8 hours after dosing, about 15% of adult women and 5% of adult men had a zolpidem level of  $\geq 50$  ng/mL, whereas for both elderly men and women, about 10% had such a zolpidem level.

FDA is continuing to evaluate the risk of next-morning impairment with other insomnia drugs.

### **Zolpidem Dosing Recommendations for Adults (Non-Elderly)**

	<b>Dosing recommendations in current drug label for zolpidem</b>	<b>FDA's proposed new dosing recommendations for zolpidem</b>
<b>Ambien, Edluar, Zolpimist</b>	<u>Men and Women:</u> 10 mg once daily, immediately before bedtime	<u>Women:</u> 5 mg once daily, immediately before bedtime  <u>Men:</u> 5 or 10 mg once daily, immediately before bedtime
<b>Ambien CR</b>	<u>Men and Women:</u> 12.5 mg once daily, immediately before bedtime	<u>Women:</u> 6.25 mg once daily, immediately before bedtime  <u>Men:</u> 6.25 or 12.5 mg once daily, immediately before bedtime

### **Insomnia Medicines**

#### **Prescription Insomnia Medicines**

<b>Generic name</b>	<b>Found in brand name(s)</b>
zolpidem tartrate	Ambien, Ambien CR, Edluar, Zolpimist, Intermezzo
butabarbital sodium	Butisol sodium
pentobarbital and carbromal	Carbrital
flurazepam hydrochloride	Dalmane
quazepam	Doral
triazolam	Halcion
eszopiclone	Lunesta
ethchlorvynol	Placidyl
estazolam	Prosom
temazepam	Restoril
ramelteon	Rozerem
secobarbital sodium	Seconal
doxepin hydrochloride	Silenor
zaleplon	Sonata

## Over-the-counter (OTC) Insomnia Medicines

Generic name	Common brand name(s)
diphenhydramine	Benadryl Also in many cold and headache combination products*
doxylamine	Unisom Also in many cold and headache combination products*

\*Be sure to always read the Drug Facts box on OTC medicines.

## Reference

1. IMS, Vector One: National (VONA) and Total Patient Tracker (TPT). Year 2011. Extracted June 2012.

## Contact FDA

1-800-332-1088

1-800-FDA-0178 Fax

## Report a Serious Problem

MedWatch Online

**Regular Mail:** Use postage-paid FDA Form 3500

**Mail to:** MedWatch 5600 Fishers Lane

Rockville, MD 20857

## Related Information

- [FDA Drug Safety Communication: Risk of next-morning impairment after use of insomnia drugs; FDA requires lower recommended doses for certain drugs containing zolpidem \(Ambien, Ambien CR, Edluar, and Zolpimist\)](#)
- [Questions and Answers](#)