

STEP THERAPY POLICY

- POLICY:** Sedative Hypnotics Step Therapy Policy
- Ambien® (zolpidem tablets – Sanofi-Aventis, generics)
 - Ambien CR® (zolpidem extended-release tablets – Sanofi-Aventis, generics)
 - Belsomra® (suvorexant tablets – Merck)
 - Dayvigo™ (lemborexant tablets - Eisai)
 - Edluar® (zolpidem 5 and 10 mg sublingual tablets – Meda Pharmaceuticals)
 - Intermezzo® (zolpidem 1.75 and 3.5 mg sublingual tablets – Transcept Pharmaceuticals/Purdue Pharma, generics)
 - Lunesta® (eszopiclone tablets – Sepracor, generics)
 - Rozerem® (ramelteon tablets – Takeda, generics)
 - Silenor® (doxepin 3 mg and 6 mg tablets – Somaxon Pharmaceuticals, generics)
 - Sonata® (zaleplon capsules – King Pharmaceuticals, generics)
 - Zolpimist® (zolpidem oral spray – NovaDel Pharma)

REVIEW DATE: 11/11/2020

OVERVIEW

Zolpidem immediate-release (IR), Edluar, Zolpimist, and zaleplon are indicated for the **short-term treatment of insomnia**.^{1,3,5,6} Zolpidem extended-release (ER), eszopiclone, Silenor, and Rozerem are also indicated for the treatment of **insomnia**, but their product labeling does not specifically limit their use to short-term.^{2,4,8,9} All of the agents in this category have been shown to decrease sleep latency. Zaleplon and Rozerem are specifically indicated for the treatment of insomnia characterized by difficulty with sleep onset.^{3,8} Zolpidem IR, zolpidem ER, Silenor, and eszopiclone have also been shown to improve sleep maintenance or increase the duration of sleep.^{1,2,4,9} Belsomra and Dayvigo are indicated for the **treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance**.^{10,11} Zolpidem sublingual tablets are indicated for use as needed for the treatment of insomnia when a **middle-of-the-night awakening is followed by difficulty returning to sleep**.⁷ However, zolpidem sublingual tablets are not indicated for treatment of middle-of-the-night insomnia when the patient has fewer than 4 hours of bedtime remaining before the planned time of waking. Doxepin is also available generically as oral capsules (10, 25, 50, 75, 100, and 150 mg) and oral solution (10 mg/mL). These higher dose formulations are recommended for use in patients with depression and/or anxiety of varying etiologies.

Eszopiclone, zaleplon, zolpidem IR, zolpidem ER, zolpidem sublingual tablets, Edluar, and Zolpimist are all non-benzodiazepine sedative hypnotics.¹⁻⁷ These agents interact with gamma-aminobutyric acid (GABA) receptor complexes located closely to benzodiazepine receptors; the chemical structures of these agents are unrelated to the benzodiazepines. All seven are schedule IV controlled substances. Rozerem, another non-benzodiazepine sedative hypnotic, is a melatonin receptor agonist.⁸ Silenor is a tricyclic compound that acts as a histamine H₁ receptor antagonist.⁹ Neither Rozerem nor Silenor are controlled substances. Belsomra and Dayvigo are orexin receptor antagonists, and both are schedule IV controlled substances.^{10,11}

In 2017, an updated American Academy of Sleep Medicine (AASM) clinical guideline for the evaluation and management of chronic insomnia in adults was published.¹² The guideline indicates that hypnotic medications, along with management of comorbidities and non-pharmacological interventions such as cognitive behavioral therapy for insomnia (CBT-I), are an important therapeutic option for chronic insomnia. The recommendations are intended as a guide for choosing a specific pharmacological agent (vs.

no treatment) for treatment of chronic insomnia in adults, when such treatment is indicated. Each of the recommendations listed is weak, meaning it reflects a lower degree of certainty in the outcome and appropriateness of the patient-care strategy for all patients but should not be construed as an indication of ineffectiveness. The guideline suggests that clinicians can use Belsomra as a treatment for sleep maintenance insomnia; eszopiclone can be used as a treatment for sleep onset and sleep maintenance insomnia; zaleplon can be used as a treatment for sleep onset insomnia; zolpidem can be used as a treatment for sleep onset and sleep maintenance insomnia; triazolam can be used as a treatment for sleep onset insomnia; temazepam can be used as a treatment for sleep onset and sleep maintenance insomnia; Rozerem can be used as a treatment for sleep onset insomnia; and Silenor can be used as a treatment for sleep maintenance insomnia. The guideline suggested that clinicians not use trazodone, tiagabine, diphenhydramine, melatonin, tryptophan, or valerian as a treatment for sleep onset or sleep maintenance insomnia. The authors note that CBT-I is a standard of care for this condition; however, the AASM guideline does not address the relative benefits of CBT-I vs. pharmacotherapy. In addition, several agents used for insomnia are on the 2019 Beers list of medications that are categorized as potentially inappropriate agents for elderly persons aged ≥ 65 years (e.g., amitriptyline, benzodiazepines, doxepin [> 6 mg/day]); zolpidem, zaleplon, and eszopiclone should also be avoided.¹³

Use in the Elderly

Although no specific adverse events (AEs) have been noted in elderly patients, changes in pharmacokinetics and/or high doses could put this population at increased risk of AEs. The general sensitivity of the elderly population to sedative hypnotics applies to all drugs with hypnotic effects.^{14,15} However, because the potential for memory/cognitive/psychomotor impairment exists (primarily at peak concentrations) with the GABA-interacting non-benzodiazepine sedative hypnotics (the long-acting agents in particular), Rozerem's unique mechanism of action may be beneficial in older patients with or at risk for memory/cognitive/psychomotor impairment. Downward dosage adjustments of zolpidem IR, zolpidem ER, Edluar, zolpidem sublingual tablets, Zolpimist, zaleplon, Silenor, and eszopiclone are recommended when used in elderly or debilitated patients.^{1-7,9} The product labeling for Rozerem does not recommend a dosage adjustment in the elderly; Rozerem has a flat dose-response curve until the 64 mg dose is reached.⁸ Belsomra and Dayvigo have been studied in patients ≥ 65 years of age, and no clinically meaningful differences in safety or effectiveness were observed between these patients and younger patients at the recommended doses.^{10,11} However, in addition to daytime somnolence, Belsomra and Dayvigo have the potential to cause sleep paralysis, hypnagogic/hypnopompic hallucinations, and cataplexy-like symptoms, which are not seen with the other agents.

POLICY STATEMENT

This program has been developed to encourage the use of a Step 1 Product prior to the use of a Step 2 Product. If the Step Therapy rule is not met for a Step 2 Product at the point of service, coverage will be determined by the Step Therapy criteria below. All approvals are provided for 1 year in duration.

Automation: A patient with a history of one Step 1 Product within the 130-day look-back period is excluded from Step Therapy. For Silenor and generic doxepin 3 mg and 6 mg tablets, a patient who is ≥ 65 years of age will not be targeted by this Step Therapy program.

Step 1: generic eszopiclone tablets, generic ramelteon tablets, generic zaleplon capsules, generic zolpidem immediate-release tablets, generic zolpidem extended-release tablets, generic zolpidem sublingual tablets

Step 2: Ambien, Ambien CR, Belsomra, Dayvigo, Edluar, Intermezzo, Lunesta, Rozerem, Silenor, generic doxepin 3 mg and 6 mg tablets, Sonata, Zolpimist

CRITERIA

1. If the patient has tried one Step 1 Product, approve a Step 2 Product.
2. If the patient has a documented history of addiction to controlled substances, approve Silenor or generic doxepin 3 mg or 6 mg tablets.
3. If the patient is ≥ 65 years of age, approve Silenor or generic doxepin 3 mg or 6 mg tablets.
4. If the patient has difficulty swallowing or cannot swallow tablets, approve Edluar or Zolpimist.
5. No other exceptions are recommended.

REFERENCES

1. Ambien[®] tablets [prescribing information]. Bridgewater, NJ: Sanofi-Aventis; August 2019.
2. Ambien CR[®] tablets [prescribing information]. Bridgewater, NJ: Sanofi-Aventis; August 2019.
3. Sonata[®] capsules [prescribing information]. New York, NY: Pfizer Inc; August 2019.
4. Lunesta[®] tablets [prescribing information]. Marlborough, MA: Sunovion Pharmaceuticals Inc.; August 2019.
5. Edluar[®] sublingual tablets [prescribing information]. Somerset, NJ: Meda Pharmaceuticals, Inc.; August 2019.
6. Zolpimist[®] oral spray [prescribing information]. Englewood, CO: Aytu BioScience, Inc.; August 2019.
7. Intermezzo[®] sublingual tablets [prescribing information]. Stamford, CT: Purdue Pharma; August 2019.
8. Rozerem[®] tablets [prescribing information]. Deerfield, IL: Takeda Pharmaceuticals, Inc; December 2018.
9. Silenor[®] tablets for oral administration [prescribing information]. Morristown, NJ: Currax Pharmaceuticals LLC; October 2010.
10. Belsomra[®] tablets [prescribing information]. Whitehouse Station, NJ: Merck & Co., Inc.; March 2020.
11. Dayvigo[™] tablets [prescribing information]. Woodcliff Lake, NJ: Eisai Inc.; April 2020.
12. Sateia MJ, Buysse DJ, Krystal AD, et al. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med.* 2017;13(2):307–349.
13. The American Geriatrics Society 2019 Beers Criteria Update Expert Panel. American Geriatrics Society 2019 updated AGS Beers criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2019;67(4):674-694.
14. Drover DR. Comparative pharmacokinetics and pharmacodynamics of short-acting hypnotics. Zaleplon, zolpidem and zopiclone. *Clin Pharmacokinet.* 2004;43(4):227-238.
15. Patel D, Steinberg J, Patel P. Insomnia in the elderly: a review. *J Clin Sleep Med.* 2018;14(6):1017-1024.