This program applies to FlexRx Open, GenRx Open, Health Insurance Marketplace, FocusRx and KeyRx formularies.

This program is a FlexRx standard and GenRx standard step therapy program.

The BCBS MN Step Therapy Supplement also applies to this program for all Commercial/HIM lines of business.

### FDA APPROVED INDICATIONS AND DOSAGE

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
<th>Dosing and Administration</th>
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</table>
| **Ambien®**<sup>a,b</sup> (zolpidem) tablets | Short-term treatment of insomnia characterized by difficulties with sleep initiation | **Initial dose:** Initial dose:  
- Women: 5 mg once nightly  
- Men: 5-10 mg once nightly  

**Max daily dose:** 10 mg once nightly

Compared to lower doses, zolpidem 10 mg (immediate release) is more likely to impair next morning activities requiring alertness (e.g., driving).

| **Ambien CR®**<sup>a,b</sup> (zolpidem CR) tablets | Treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance | **Initial dose:**  
- Women: 6.25 mg once nightly  
- Men: 6.25-12.5 mg once nightly  

**Max daily dose:** 12.5 mg once nightly

Compared to lower doses, zolpidem 12.5 mg (extended release) is more likely to impair next morning activities requiring alertness (e.g., driving).

| **Belsomra®**<sup>a</sup> (suvorexant) tablets | Treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance | **Initial dose:** 10 mg once nightly  

**Max daily dose:** 20 mg once nightly

| **Dayvigo™**<sup>a</sup> (lemborexant) tablet | Treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance | **Initial dose:** 5 mg once nightly  

**Max daily dose:** 10 mg once nightly

| **Edluar®**<sup>a</sup> (zolpidem) sublingual tablets | Short-term treatment of insomnia characterized by difficulties with sleep initiation | **Initial dose:**  
- Women: 5 mg once nightly  
- Men: 5-10 mg once nightly  

**Max daily dose:** 10 mg once nightly

Compared to lower doses, zolpidem 10 mg (immediate release) is more likely to impair next morning activities requiring alertness (e.g., driving).
| **Intermezzo**<sup>a,b</sup> (zolpidem)<sup>a</sup>  
sublingual tablet | For use as needed for the treatment of insomnia when a middle of the night awakening is followed by difficulty returning to sleep | **Max daily dose:**  
• Women: 1.75 mg once nightly  
• Men: 3.5 mg once nightly |
| **Lunesta**<sup>a,b</sup> (eszopiclone)<sup>a</sup>  
tablet | Treatment of insomnia | **Initial Dose:** 1 mg once nightly  
**Max daily dose:** 3 mg once nightly  
Compared to lower doses, eszopiclone 2 mg and 3 mg increase the risk of next day impairment of driving and other activities that require full alertness. |
| **Rozerem**<sup>b</sup> (ramelteon)<sup>b</sup>  
tablet | Treatment of insomnia characterized by difficulty with sleep onset | **Initial dose:** 8 mg once nightly  
**Max daily dose:** 8 mg once nightly |
| **Silenor**<sup>b</sup> (doxepin)<sup>b</sup>  
tablet | Treatment of insomnia characterized by difficulty with sleep maintenance | **Initial dose:** 6 mg once nightly. 3 mg once nightly may be appropriate for some patients.  
**Max daily dose:** 6 mg once nightly |
| **Sonata**<sup>a,b</sup> (zaleplon)<sup>a</sup>  
capsule | Short-term treatment of insomnia | **Initial Dose:** 10 mg once nightly  
**Max daily dose:** 20 mg once nightly |
| **Zolpimist**<sup>a</sup> (zolpidem)<sup>a</sup>  
oral spray | Short-term treatment of insomnia characterized by difficulties with sleep initiation | **Initial dose:**  
• Women: 5 mg once nightly  
• Men: 5-10 mg once nightly  
**Max daily dose:** 10 mg once nightly  
Compared to lower doses, zolpidem 10 mg (immediate release) is more likely to impair next-morning activities requiring alertness (e.g., driving). |

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**CLINICAL RATIONALE**

Insomnia is the most prevalent sleep disorder and can be associated with numerous adverse effects on function, health, and quality of life.<sup>11,13</sup> The American Academy of Sleep Medicine and the American College of Physicians created clinical guidelines for the management (psychological/behavioral and pharmacological).<sup>11,12,13</sup> The guidelines indicate psychological/behavioral interventions are first line and as effective as pharmacologic therapies.<sup>11,12</sup> Short-term hypnotic therapy should be supplemented with behavioral and cognitive therapies. The guidelines recommend these general sequence of medication trials for patients with primary insomnia:<sup>11</sup>

- Short-intermediate acting benzodiazepine receptor agonists (BZD or newer BzRAs) or ramelteon: examples of these medications include zolpidem, eszopiclone, zaleplon, and temazepam
- Alternate short-intermediate acting BzRAs or ramelteon if the initial agent has been unsuccessful
• Sedating antidepressants, especially when used in conjunction with treating comorbid depression/anxiety: examples of these include trazodone, amitriptyline, doxepin, and mirtazapine
• Combined BzRA or ramelteon and sedating antidepressant
• Other sedating agents: examples include anti-epilepsy medications (gabapentin, tiagabine) and atypical antipsychotics (quetiapine and olanzapine)

The guidelines also provide recommendations regarding the management of chronic insomnia with all prescription medications:

• Pharmacological treatment should be accompanied by patient education regarding: (1) treatment goals and expectations; (2) safety concerns; (3) potential side effects and drug interactions; (4) other treatment modalities (cognitive and behavioral treatments); (5) potential for dosage escalation; (6) rebound insomnia.
• Patients should be followed on a regular basis, every few weeks in the initial period of treatment when possible, to assess for effectiveness, possible side effects, and the need for ongoing medication.
• Efforts should be made to employ the lowest effective maintenance dosage of medication and to taper medication when conditions allow.
  o Medication tapering and discontinuation are facilitated by cognitive behavioral therapy for insomnia.
• Chronic hypnotic medication may be indicated for long-term use in those with severe or refractory insomnia or chronic comorbid illness. Whenever possible, patients should receive an adequate trial of cognitive behavioral treatment during long-term pharmacotherapy.
  o Long-term prescribing should be accompanied by consistent follow-up, ongoing assessment of effectiveness, monitoring for adverse effects, and evaluation for new onset or exacerbation of existing comorbid disorders
  o Long-term administration may be nightly, intermittent (e.g., three nights per week), or as needed.

Use in the Elderly
Zolpidem, zaleplon, and eszopiclone are all included in the list of Potentially Inappropriate Medications (for use in the elderly) in the Beers List published by the American Geriatrics Society. Benzodiazepine-receptor agonist hypnotics (i.e., Z drugs) have adverse events similar to those of benzodiazepines in older adults (e.g., delirium, falls, fractures); increased emergency room visits and hospitalizations; motor vehicle crashes; minimal improvement in sleep latency and duration. Beers provides a strong recommendation that these drugs be avoided in the elderly.

REFERENCES


Insomnia Agents Step Therapy

TARGET AGENTS
- Ambien® (zolpidem)\textsuperscript{a}
- Ambien CR® (zolpidem)\textsuperscript{a}
- Belsomra® (suvorexant)
- Dayvigo™ (lemborexant)
- Edluar® (zolpidem)
- Intermezzo® (zolpidem)\textsuperscript{a}
- Lunesta® (eszopiclone)\textsuperscript{a}
- Rozerem® (ramelteon)\textsuperscript{b}
- Silenor® (doxepin)\textsuperscript{b}
- Sonata® (zaleplon)\textsuperscript{a}
- Zolpimist™ (zolpidem)

\textsuperscript{a} – generic available that is a prerequisite agent for step therapy program
\textsuperscript{b} – generic available

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Brand Insomnia Agents will be approved when ONE of the following is met:

1. The patient is currently being treated with the requested agent as indicated by ALL of the following:
   a. A statement by the prescriber that the patient is currently taking the requested agent
   \textbf{AND}
   b. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
   \textbf{AND}
   c. The prescriber states that a change in therapy is expected to be ineffective or cause harm
   \textbf{OR}

2. The patient’s medication history includes the use of a generic nonbenzodiazepine hypnotic agent within the past 999 days
   \textbf{OR}

3. BOTH of the following:
   a. The prescriber has stated that the patient has tried a generic nonbenzodiazepine hypnotic agent
   \textbf{AND}
   b. Generic nonbenzodiazepine hypnotic agent was discontinued due to lack of effectiveness or an adverse event
   \textbf{OR}

4. The patient has an intolerance, FDA labeled contraindication, or hypersensitivity to ALL available generic nonbenzodiazepine hypnotic agents
   \textbf{OR}

5. The prescriber has provided documentation that ALL generic nonbenzodiazepine hypnotic agents cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm
   \textbf{OR}

6. The requested agent is a non-controlled agent AND the patient requires therapy with the non-controlled agent

Length of Approval: 12 months
NOTE: If Quantity Limit program also applies, please refer to Quantity Limit documents.