# Insomnia Agents Step Therapy Criteria

## FDA APPROVED INDICATIONS AND DOSAGE

<table>
<thead>
<tr>
<th>Available Products</th>
<th>Indications&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Dosing and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambien (zolpidem)&lt;sup&gt;bc&lt;/sup&gt;</td>
<td>For short-term treatment of insomnia characterized by difficulties with sleep initiation. Showed to decrease sleep latency for up to 35 days in controlled clinical studies. Clinical trials supporting efficacy were 4-5 weeks in duration with final formal assessments of sleep latency performed at the end of treatment.</td>
<td>10 mg once daily immediately before bedtime; 5 mg once daily in elderly or debilitated patients; Dosage should be individualized Maximum daily dose is 10 mg</td>
</tr>
<tr>
<td>Ambien CR (zolpidem CR)&lt;sup&gt;bc&lt;/sup&gt;</td>
<td>For insomnia characterized by difficulties with sleep onset and/or sleep maintenance (as measured by wake time after sleep onset). Clinical trials performed in support of efficacy were up to 3 weeks &amp; 24 wks in duration.</td>
<td>12.5 mg once daily immediately before bedtime. Elderly or debilitated patients should be started at 6.25 mg immediately before bedtime. Total dose should not exceed 12.5 mg per day.</td>
</tr>
<tr>
<td>Edluar (zolpidem sublingual tablets)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>For short-term treatment of insomnia characterized by difficulties with sleep initiation. Clinical trials supporting efficacy were 4-5 weeks in duration with final formal assessments of sleep latency performed at the end of treatment.</td>
<td>10 mg once daily immediately before bedtime; 5 mg once daily in elderly or debilitated patients; Dosage should be individualized Maximum daily dose 10 mg.</td>
</tr>
<tr>
<td>Lunesta (eszopiclone)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>For treatment of insomnia; shown to decrease sleep latency and improve sleep maintenance. Clinical trials performed in support of efficacy were up to 6 months in duration. Final formal assessments of sleep latency and maintenance were performed at 4 weeks in the 6-week study, at the end of both 2-week studies and at the end of the 6-month study.</td>
<td>Initial dose of 2 mg immediately before bedtime; Dose may be increased to 3 mg if indicated. Initial dose of 1 mg in elderly patients, may be increased to 2 mg if indicated. Dosage should be individualized</td>
</tr>
<tr>
<td>Rozerem (ramelteon)</td>
<td>For insomnia characterized by difficulty with sleep onset. Clinical trials performed in support of efficacy were up to 6 months in duration. Final formal assessments of sleep latency were performed after 2 days of treatment during the crossover study, at 5 weeks in the 6-week studies, and at the end of the 6-month study.</td>
<td>8 mg taken within 30 minutes of going to bed. Total Rozerem dose should not exceed 8 mg per day.</td>
</tr>
</tbody>
</table>

<sup>a</sup> Prescribing information for all products contains the following: Failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated.

<sup>b</sup> Hypnotics classified as Schedule IV controlled substances

<sup>c</sup> Generics available
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<tr>
<td><strong>Silenor</strong>&lt;br&gt;(doxepin)</td>
<td>For the treatment of insomnia characterized by difficulty with sleep maintenance.&lt;br&gt;The clinical trials performed in support of efficacy were up to 3 months in duration.</td>
<td>6 mg once daily; a 3 mg once daily dose may be appropriate for some patients. The recommended starting dose in elderly patients is 3 mg once daily. Dosage should be individualized Maximum daily dose is 6 mg.</td>
</tr>
<tr>
<td><strong>Sonata</strong>&lt;br&gt;(zaleplon)&lt;sup&gt;bc&lt;/sup&gt;</td>
<td>For short-term treatment of insomnia.&lt;br&gt;Shown to decrease the time to sleep onset for up to 30 days in controlled clinical studies. Not shown to increase total sleep time or decrease the number of awakenings. Clinical trials performed in support of efficacy ranged from a single night to 5 weeks in duration. Final formal assessments of sleep latency were performed at the end of treatment.</td>
<td>10 mg once daily; 5 mg once daily may be sufficient for low weight individuals and elderly or debilitated patients; 20 mg may be considered for occasional patients not responding to lower doses Dosage should be individualized Maximum daily dose is 20 mg (10 mg in elderly)</td>
</tr>
<tr>
<td><strong>Zolpimist</strong>&lt;br&gt;(zolpidem oral spray)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>For short-term treatment of insomnia characterized by difficulties with sleep initiation.&lt;br&gt;Shown to decrease sleep latency for up to 35 days in controlled clinical studies. Clinical trials performed in support of efficacy were 4-5 weeks in duration with final formal assessments of sleep latency performed at the end of treatment.</td>
<td>10 mg once daily immediately before bedtime; 5 mg once daily in elderly or debilitated patients; Dosage should be individualized Maximum daily dose is 10 mg</td>
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<sup>a</sup> – Prescribing information for all products contains the following: Failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated.

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**CLINICAL RATIONALE**

According to guidelines on management of chronic insomnia in the United States (2008), treatment is recommended when the chronic insomnia has a significant impact on patient sleep quality, health, comorbid conditions, or daytime function. It is essential to recognize and treat comorbid conditions that commonly occur with insomnia, and to identify and modify behaviors and medications or substances that impair sleep. Psychological/behavioral interventions and benzodiazepine receptor agonists have shown short-term efficacy for the treatment of chronic insomnia. However, psychological and behavioral interventions have also shown long-term efficacy and can be used for both primary and comorbid insomnias. Psychological/behavioral interventions and pharmacological intervention may be used alone or in combination. Short-term hypnotic therapy should be supplemented with behavioral and cognitive therapies when possible.<sup>8</sup>

**Choice of Hypnotic:** First line pharmacotherapies include short/intermediate acting benzodiazepine receptor agonists (e.g., zaleplon, zolpidem, eszopiclone, temazepam), or ramelteon. No specific agent within this group is recommended over the others in a general sense. However, individual patients may respond differentially to different medications within this class. If a patient does not respond well to the initial agent, a different agent within the same class is considered appropriate. Sedating low-dose antidepressants (e.g., doxepin, trazodone, mirtazapine, amitriptyline, etc.) are considered third-line after the other agents have failed, especially when used in conjunction with treating comorbid depression and/or
anxiety. Evidence for their efficacy when used alone is relatively weak. No specific agent within this group is recommended as preferable to the others in the group. Data suggests that tricyclic antidepressants (e.g., doxepin, amitriptyline) may improve sleep efficiency but have the potential for adverse anticholinergic effects, daytime sedation, and suppression of rapid eye movement (REM) sleep.

**Duration of Use:** In clinical practice, hypnotic medications are often used over durations of one to twelve months without dosage escalation, but the empirical data base for long-term use remains small. Randomized controlled trials of eszopiclone or zolpidem have shown continued efficacy without significant complications for 6 months, and in open-label extension studies for 12 months or longer. For many patients, an initial treatment period of 2-4 weeks may be appropriate, followed by re-evaluation of the continued need for treatment. A subset of patients with severe chronic insomnia may be appropriate for longer term or chronic maintenance treatment, but the specific defining characteristics of these patients are unknown.

If hypnotics are used long-term, regular follow up visits should be scheduled at least every 6 months in order to monitor efficacy, side effects, tolerance, and abuse/misuse of medications. Periodic attempts to reduce the frequency and dose in order to minimize side effects and determine the lowest effective dose may be indicated.

**Discontinuation:** Rebound insomnia and withdrawal can be minimized by gradually tapering the dose and frequency of use. Tapering and discontinuation of hypnotic medication is facilitated by concurrent application of cognitive behavioral therapies, which increase rates of successful discontinuation and duration of abstinence.

Guidelines in the United Kingdom (2009) on treatment of short-term insomnia (<4 weeks), suggest that any potential causes of insomnia or comorbidities should first be addressed. Advise on good sleep hygiene. There is insufficient evidence to assess the effectiveness of sleep hygiene as a single intervention; however its use is widely supported in current literature and guidelines. If daytime impairment is severe, consider a short course of a hypnotic drug.

There is good evidence for efficacy of hypnotic drugs in treatment of short-term insomnia; however, their use is associated with adverse effects (e.g., daytime sedation, poor motor coordination, cognitive impairment, driving accidents, and falls). Use the lowest effective dose for the shortest possible period. Treatment should not continue longer than 2 weeks. Review after 2 weeks and consider referral for cognitive behavioral therapy if symptoms persist. Recommended hypnotics include short-acting benzodiazepines (temazepam) and non-benzodiazepines (zopiclone [not available in the U.S.], zolpidem, zaleplon). If there is no response to one hypnotic do not prescribe another. If the person has adverse effects considered directly related to the hypnotic, consider switching to another hypnotic. There is a lack of compelling evidence to distinguish between these drugs in their efficacy, adverse effects, or dependency. Sedative drugs other than hypnotics (e.g., antidepressants, antihistamines, chloral hydrate, clomethiazole, barbiturates) are not recommended for the management of insomnia. Expert opinion from reviews suggests that there is insufficient evidence to support their use, and that the potential for adverse effects is significant.

For long-term insomnia (>4 weeks), manage the underlying cause of insomnia and related comorbidities. Cognitive and behavioral therapies are recommended first line. Advise good sleep hygiene, and regular exercise in addition to cognitive and behavioral interventions. Hypnotics are generally not recommended for management of long-term insomnia. There is a lack of evidence for long-term use and there are concerns regarding safety. Long-term use of hypnotics can lead to tolerance, physical dependence, adverse effects on withdrawal, rebound insomnia, and increased mortality.
For additional clinical information see Prime Therapeutics Formulary Chapters 9.4D: Hypnotics: Non-Benzodiazepine GABA-Receptor Modulators; and 9.4E: Selective Melatonin Receptor Agonist.

REFERENCES

Document History
Original Prime Standard criteria approved by External UMC 0207
Initial Client Review, Client Specific Criteria approved by HCSC Corporate Clinical Committee 04/2007
Annual Review Prime Standard criteria approved by External UM Committee 05/2008
Client Specific Annual Review, Client Specific Criteria approved by HCSC Corporate Clinical Committee 06/2008
Annual Review Prime Standard criteria with changes approved by P&T UM Committee 05/2009
Client Specific Annual Review, Client Specific criteria approved by HCSC Corporate Clinical Committee 06/2009
Annual Review Prime Standard criteria with changes approved by P&T UM Committee 05/2010
Client Specific Annual Review, Client Specific Criteria approved by HCSC Corporate Clinical Committee 09/2010
Administrative Addition (addition of generic zolpidem ER 6.25 mg) 10/2010
Insomnia Agents Step Therapy

OBJECTIVE
The intent of the Insomnia Agents Step Therapy (ST) program is to encourage the use of cost-effective generic insomnia agents over the more expensive brand agents and to accommodate for use of brand nonbenzodiazepine benzodiazepine receptor agonists (NBRAs - Ambien, Ambien CR, Edluar, Lunesta, Sonata, and Zolpimist), the melatonin receptor agonist Rozerem, and the histamine H1 receptor antagonist Silenor when generic agents cannot be used due to previous trial and failure, allergy, intolerance, or contraindication. Patients who are receiving a brand insomnia agent will be approved for continuation of that agent. If the patient cannot be treated with a controlled substance, Rozerem or Silenor may be approved for use. All dosage forms of the brand drugs listed will be included as targets in the step therapy program.

TARGET DRUGS
- Ambien® (zolpidem)a
- Ambien CR® (zolpidem)a
- Edluar® (zolpidem)
- Lunesta® (eszopiclone)
- Rozerem® (ramelteon)
- Silenor® (doxepin)
- Sonata® (zaleplon)a
- Zolpimist® (zolpidem)b
  a – generic available that is a prerequisite agent for step therapy program
  b - approved by the FDA; will be included in program if/ when marketed

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Insomnia Agents will be approved when ANY ONE of the following is met:
1. The patient is currently receiving the requested brand agent OR
2. The patient’s medication history includes use of a generic nonbenzodiazepine benzodiazepine receptor agonist (NBR) insomnia agent (generic zolpidem immediate-release, zolpidem extended-release or zaleplon) OR
3. The patient has a contraindication, allergy, or intolerance, to the available generic NBRA insomnia agents OR
4. The patient requires therapy with the noncontrolled agent, Rozerem or Silenor

Length of Approval: 12 months
Insomnia Agents Step Therapy

**ELECTRONIC EDIT**
For the insomnia agents step therapy edit, the 90-day search period was chosen to capture the most recent or current therapy for one preferred agent.

**SUMMARY OF INSOMNIA AGENTS STEP THERAPY**

<table>
<thead>
<tr>
<th>Targeted Agent(s)</th>
<th>Ambien, Ambien CR, Edluar, Lunesta, Rozerem, Silenor, Sonata, Zolpimist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is auto-grandfathering implemented? (with look-back time frame)</td>
<td>Y (90 days⁴)</td>
</tr>
<tr>
<td>Prerequisite Agent(s)</td>
<td>generic zolpidem (immediate-release/IR and extended-release/ER), generic zaleplon</td>
</tr>
<tr>
<td>Number of prerequisites required</td>
<td>1</td>
</tr>
<tr>
<td>Prerequisite look-back time frame</td>
<td>90 days⁴</td>
</tr>
<tr>
<td>Age-related edit?</td>
<td>NA</td>
</tr>
<tr>
<td>Additional comments</td>
<td>NA</td>
</tr>
</tbody>
</table>

For auto-grandfathering, ANY ONE of: Ambien, Ambien CR, Edluar, Lunesta, Rozerem, Silenor, Sonata, Zolpimist

<table>
<thead>
<tr>
<th>GPIs (multisource code)</th>
<th>602040******** 602500******** 604000******** (GPI for Zolpimist will be included when available) (M, N, or O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>For Prerequisites, ANY ONE of: generic zolpidem (IR or ER), generic zaleplon</td>
<td>602040******** (Y)</td>
</tr>
<tr>
<td>Prerequisite look-back time frame:</td>
<td>90 days⁴</td>
</tr>
</tbody>
</table>

**DETAILS OF INSOMNIA AGENTS STEP THERAPY**

**PRIOR AUTHORIZATION CRITERIA QUESTION SET**

**Initial and Renewal Evaluation**

1. Is the patient currently being treated with the requested brand NBRA, Rozerem, or Silenor?
   If yes, approve for 12 months. If no, continue to 2.

① - The system searches for a claim with a days supply that begins or ends in the past 90 days. For claims with a 30-day supply the system would be able to identify a claim processed for payment between 1 and 120 days prior to the new claim. For claims that are dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 180 days.
2. Does the patient’s medication history indicate previous use of an available generic nonbenzodiazepine benzodiazepine receptor agonist (NBRA)?
   If yes, approve for 12 months. If no, continue to 3.

3. Does the patient have an allergy, intolerance, contraindication, or treatment failure to generic NBRA therapy?
   If yes, approve for 12 months. If no, continue to 4.

4. Does the patient require a noncontrolled agent for the treatment of insomnia?
   If yes, continue to 5. If no, deny.

5. Is the requested agent Rozerem or Silenor?
   If yes, approve for 12 months. If no, deny.