This policy has been developed through review of medical literature, consideration of medical necessity, generally accepted medical practice standards, and approved by the IEHP Pharmacy and Therapeutics Subcommittee.

**Class:** Hypnotics  
**Formulary Drugs:** zolpidem (Ambien), temazepam (Restoril)  
**Non-Formulary Drugs:** zolpidem (Ambien CR), zolpidem sublingual (Edluar, Intermezzo), zolpidem mucous membrane spray (Zolpimist), zaleplon (Sonata), eszopiclone (Lunesta), ramelteon (Rozerem), suvorexant (Belsomra), doxepin (Silenor), flurazepam (Dalmane)  
**LOB:** Non-medicare  
**Effective date:** February 17, 2016  
**Revision Date:** February 17, 2016

**Policy/Criteria:**

1. Non-formulary hypnotic agents for short-term treatment of insomnia:  
   a. Failure or contraindication to the first line formulary alternative: zolpidem  
   b. Failure or contraindication to ONE of preferred non-formulary alternatives: zaleplon (Sonata) or eszopiclone (Lunesta)  
   c. Rozerem may be medically necessary for members with documented substance abuse issues  
   d. Authorization will be issued for 6 months

2. Quantity Limit based on gender and initiation (Zolpidem Products Only):  
   a. Male: 10mg/day for immediate release zolpidem and 12.5mg/day for Ambien CR  
   b. Women: 5mg/day for immediate release zolpidem and 6.25mg/day for Ambien CR (based on FDA recommendation)

**Clinical Justification:**

JCSM 2008: Clinical Guideline for the Evaluation and Management of Chronic Insomnia in Adults:

- Short-term hypnotic treatment should be supplemented with behavioral and cognitive therapies and patient education when possible  
- When pharmacotherapy is utilized, the choice of a specific pharmacological agent within a class, should be directed by: (1) symptom pattern; (2) treatment goals; (3) past treatment responses; (4) patient preference; (5) cost; (6) availability of other treatments; (7) comorbid condition; (8) contraindications; (9) concurrent medication interactions; and (10) side effects  
- The recommended general sequence of medication trials for primary insomnia is:

   1) Short-intermediate acting benzodiazepine receptor agonists (e.g. zolpidem, eszopiclone, zaleplon and temazepam) or ramelteon
2) Alternate short-intermediate acting benzodiazepine receptor agonists or ramelteon if the initial agent has been unsuccessful.

3) Sedating antidepressants, especially when used in the management of comorbid depression or anxiety, may be tried next (e.g. trazodone, amitriptyline, doxepin, mirtazapine).

4) The next step can be combined use of a sedating antidepressant with a benzodiazepine receptor agonist or ramelteon.

5) Anti-epilepsy medications (e.g. gabapentin, tiagabine) and atypical antipsychotics (e.g. quetiapine, olanzapine) should only be used in patients with comorbid insomnia who may benefit from the primary action of the drugs as well as from their sedating effects.

- Employ lowest effective maintenance dosage of medication and to taper medication when conditions allow. Medication tapering and discontinuation are facilitated by cognitive behavioral therapy.
- Chronic hypnotic medication along with an adequate trial of cognitive behavioral treatment may be indicated for long term use in those with severe or refractory insomnia or chronic comorbid illness.

**Pharmacological Agents:**

- Short to intermediate-acting Benzodiazepine Receptor Agonistic Modulators or Ramelteon:
  - No specific agent within this group is recommended as preferable to the others
  - Zaleplon and ralmelteon with very short half-lives are likely to reduce sleep latency but have little effect on waking after sleep onset, and less likely to result in residual sedation.
  - Eszopiclone and temazepam with relatively longer half-lives, are more likely to improve sleep maintenance, and more likely to produce residual sedation.
  - Triazolam has been associated with rebound anxiety, and thus is not considered a first line hypnotics
  - Patients with a history of substance use disorders may be appropriate candidates for ramelteon, particularly for sleep initiation difficulty.

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<tr>
<th>Drug</th>
<th>Recommended Dosage</th>
<th>Indications/Comments</th>
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<tbody>
<tr>
<td><strong>Nonbenzodiazepine Receptor Agonists</strong></td>
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| zolpidem (Ambien), zolpidem SL (Edluar, Zolpimist) | †5-10mg hs (max 10mg/day) | - Short-term treatment of insomnia  
  - Primarily used for sleep-onset |
| zolpidem SL (Intermezzo) | Δ1.75-3.5mg as directed | - Treatment of insomnia, middle-of-the-night awakening, at least 4 hours of bedtime remaining |
| zolpidem (Ambien CR)   | Ø6.25-12.5mg hs     | - Sleep-onset and/or sleep maintenance insomnia  
  - Efficacy shown up to 24 week duration in clinical trials |
| zaleplon (Sonata)      | 5-10mg hs; max 20mg | - Short-term treatment of insomnia  
  - Primarily used for sleep-onset |
| eszopiclone (Lunesta)  | 1mg initially, may increase to 2-3mg if | - Sleep-onset and sleep maintenance insomnia  
  - Efficacy shown up to 6 month duration in clinical trials |
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<th>Drug Class</th>
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<th>Indications</th>
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<tr>
<td><strong>Tricyclic antidepressant</strong></td>
<td>Doxepine (Silenor)</td>
<td>3-6mg hs</td>
<td>Treatment of insomnia characterized by difficulties with sleep maintenance</td>
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<td><strong>Benzodiazepine</strong></td>
<td>Temazepam (Restoril)</td>
<td>7.5-30mg hs; max 30mg</td>
<td>Short-term treatment of insomnia</td>
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<td>Relatively longer half-life, and are more likely to improve sleep maintenance</td>
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<td><strong>Melatonin Agonist</strong></td>
<td>Ramelteon (Rozerem)</td>
<td>8mg hs</td>
<td>Sleep-onset insomnia</td>
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<td>Efficacy shown up to 6 month duration in clinical trials</td>
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<td>May consider for patients with history of substance abuse</td>
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<tr>
<td><strong>Orexin Receptor Antagonist</strong></td>
<td>Suvorexant (Belsomra)</td>
<td>10mg initially (may increase to 15-20mg)</td>
<td>Sleep-onset and sleep maintenance insomnia</td>
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<td>Reports of daytime sleepiness, next-day impairment due to long half-life of 12 hours</td>
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<td>Avoid concurrent use of CYP3A strong inhibitors or inducers</td>
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\(\Delta\) Recommended dose in women is 1.75mg; \(\diamond\) Recommended dose in women is 6.25mg; \(^{+}\) Recommended dose in women is 5mg

**Summary:**

- According to JCSM guideline, first line treatment for insomnia include short to intermediate acting benzodiazepine receptor agonist (e.g. zolpidem, zaleplon, temazepam) and ramelteon. In general, common adverse effects for hypnotic agents include residual daytime sedation, dizziness, cognitive and motor-coordination impairment. Non-benzodiazepine agonists (e.g. zaleplon, zolpidem) and ramelteon have relatively shorter half-life than benzodiazepine, and thus often associated with less adverse effects. However, in light of FDA safety communication, next-morning impairment has been increasingly recognized with higher doses in certain patient population.

  a. FDA Medwatch Warning (Dated: Jan 10, 2013): FDA recommends initial 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) based on recent safety information.
  b. FDA warning to advise patients refrain from driving or activities that require mental alertness the day after taking zolpidem extended release.
  c. FDA safety communication to caution that eszopiclone 2 and 3mg dose may associate with impairment in driving, memory and coordination. Thus, the initial dose should be 1mg for all patients.

- It is recommended to employ lowest effective maintenance dosage of medication and to taper medication when conditions allow, along with cognitive behavioral therapy when indicated.
- Ramelteon (Rozerem) is the first hypnotic that is not classified as a controlled substance, with low abuse potential, which may be a therapeutic option for patients with a history of drug abuse.
References