BlueCross BlueShield of Illinois †

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Insomnia Agents
Step Therapy Criteria

Program may be implemented with the following options:
1) Option 1: generic insomnia agent before brand insomnia agent OR
2) Option 2: generic insomnia agent before preferred brand AND generic insomnia agent and preferred brand agent before nonpreferred brand insomnia agent

For BlueCross BlueShield of Illinois, BlueCross BlueShield of New Mexico, BlueCross BlueShield of Oklahoma, or BlueCross BlueShield of Texas, Option 1 (one-step, generic insomnia agent before brand insomnia agent) will apply.

Brand	Generic	Dosage Form
Ambien®	zolpidem	oral tablets[a]
Ambien CR®	zolpidem	extended-release oral tablets
Edluar [b]	zolpidem	sublingual tablets
Lunesta®	eszopiclone	oral tablets
Rozerem®	ramelteon	oral tablets
Sonata®	zaleplon	oral capsules[a]
Zolpimist™ [b]	zolpidem	oral spray

[a] available as a generic and included in the program
[b] approved by the FDA; will be included in program if/ when marketed

FDA APPROVED INDICATIONS[1-7]

The following information is taken from individual drug prescribing information and is provided here as background information only. Not all FDA-approved indications may be considered medically necessary. All criteria are found in the section "Prior Authorization Criteria for Approval."

Ambien®[1]

Ambien® (zolpidem) is indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. Ambien has been shown to decrease sleep latency for up to 35 days in controlled clinical studies.

The clinical trials performed in support of efficacy were 4-5 weeks in duration with the final formal assessments of sleep latency performed at the end of treatment.

Ambien CR®[2]

Ambien CR® (zolpidem extended-release) is indicated for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance (as measured by wake time after sleep onset).

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The clinical trials performed in support of efficacy were up to three weeks (using polysomnography measurement up to 2 weeks in both adult and elderly patients) and 24 weeks (using patient-reported assessment in adult patients only) in duration.

Edluar[3]
Edluar (zolpidem) sublingual tablets are indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. Zolpidem has been shown to decrease sleep latency for up to 35 days in controlled clinical studies.

Lunesta®[4]
Lunesta® (eszopiclone) is indicated for the treatment of insomnia. In controlled outpatient and sleep laboratory studies, Lunesta administered at bedtime decreased sleep latency and improved sleep maintenance.

The clinical trials performed in support of efficacy were up to 6 months in duration. The 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.

Rozerem®[5]
Rozerem® (ramelteon) is indicated for treatment of insomnia characterized by difficulty with sleep onset.

The clinical trials performed in support of efficacy were up to 6 months in duration. The 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.

Sonata®[6]
Sonata® (zaleplon) is indicated for the short-term treatment of insomnia. Sonata has been shown to decrease the time to sleep onset for up to 30 days in controlled clinical studies. It has not been shown to increase total sleep time or decrease the number of awakenings.

The clinical trials performed in support of efficacy ranged from a single night to 5 weeks in duration. The final formal assessments of sleep latency were performed at the end of treatment.

Zolpimist™[7]
Zolpimist™ (zolpidem) oral spray is indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. Zolpidem has been shown to decrease sleep latency for up to 35 days in controlled clinical studies.

The clinical trials performed in support of efficacy were up to 4 to 5 weeks in duration with the final formal assessments of sleep latency performed at the end of treatment.

RATIONALE FOR STEP THERAPY

The intent of the step therapy criteria for the nonbenzodiazepine benzodiazepine receptor agonists (NBRAs), (Ambien, Ambien CR, Edluar, Lunesta, Sonata, and Zolpimist), and the melatonin receptor agonist Rozerem, is to encourage the use of the more cost-effective generic agents prior to use of the brand agents. The program has been developed with the opportunity to implement one of two options; 1) a one-step edit that requires therapy with a generic insomnia agent before any brand or 2) a two-step edit that requires use of a generic insomnia agent before use of a preferred brand agent (included in manufacturer rebate program) and therapy with both a generic and a preferred brand insomnia agent when a nonpreferred brand is requested.

Insomnia has been defined by complaints of disturbed sleep when there is adequate opportunity and circumstance for sleep.[8] The condition may consist of difficulty with initiation, maintenance, duration, or quality of sleep that results in impairment of daytime functioning.[8] Insomnia may increase the risk of

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depression or result in poor memory, reduced concentration, or poor work performance[9] Most cases of insomnia occur with other conditions such as psychiatric disorders, particularly depression and substance abuse, cardiopulmonary disorders, and conditions with somatic components that disrupt sleep (e.g., pain).[8]Other sleep disorders (e.g., obstructive sleep apnea, restless legs syndrome, periodic limb movement disorder) may also contribute to insomnia. [8] Symptoms may occur acutely (less than four weeks duration) or symptoms may be chronic. Definitions for chronic insomnia have varied from study to study, with minimum durations ranging from thirty days to as long as six months.[9]

Treatment options for insomnia include both cognitive behavioral therapies and pharmacologic therapies. [8-13] While behavioral and cognitive-behavioral therapies have demonstrated efficacy, few clinicians are experts, and these techniques are not widely used. [8] Management of insomnia has traditionally involved pharmacotherapy. [10] Classes of prescription medications used include benzodiazepines, NBRAs, sedating antidepressants, and melatonin receptor agonists.[8-10,13] [see also Chapter 9.4d: Hypnotics: Nonbenzodiazepine GABA-Receptor Modulators[19] and Chapter 9.4e: Hypnotics: Selective Melatonin Receptor Agonists.[20]] Nonprescription sedating antihistamines are marketed for treatment of insomnia although efficacy of these agents is not well-supported by clinical studies. [8]

Guidelines from professional societies and consensus statements recommend NBRAs as agents of first choice in the pharmacologic treatment of insomnia.[8,10,14,15] The National Institute for Clinical Excellence (NICE) in its guidance on the use of zaleplon, zolpidem, and zopiclone (not available in the US) for the short-term management of insomnia found some statistically significant differences between these agents and the benzodiazepines for some of the efficacy outcome measures, but the differences were not consistent across trials. [12] In most cases, the absolute difference was small and the clinical significance of these differences was difficult to determine.[12]

A drug class review on the newer agents for treatment of insomnia by the Oregon Evidence-based Practice Center also found that there were some differences between agents on some outcomes.[9] No one drug appeared to be consistently superior. In head-to-head trials zaleplon and zolpidem were similarly effective for sleep latency, but zolpidem was more likely to result in improvement in quality of sleep at the end of treatment. These agents were similar for daytime alertness. In two head-to-head trials, zaleplon was less likely than zolpidem to cause rebound insomnia. One head-to-head trial comparing zolpidem and eszopiclone demonstrated similar objective sleep latency and Wake Time After Sleep Onset measured by polysomnography after two nights of treatment. There were no differences between agents on subjective measures of next day effects, including morning sleepiness, daytime alertness, and daytime ability to function.[9]

There are no head-to-head trials comparing zolpidem extended-release to the other NBRAs and only one placebo-controlled trial has been published. This trial evaluated the long-term efficacy and safety of zolpidem extended-release 12.5 mg, administered three to seven nights per week for 24 weeks, in patients with chronic primary insomnia.[16] Findings from the study establish the efficacy of zolpidem extended-release 12.5 mg for up to six months.[16] Treatment provided sustained and significant improvements in sleep onset (sleep onset latency, $p \leq 0.0014$ for zolpidem extended-release versus placebo) and maintenance (night time awakenings, $p < 0.0001$ for zolpidem extended-releases versus placebo) and also improved next-day concentration and morning sleepiness ($p = 0.0014$ for zolpidem extended-release versus placebo).[16] The Food and Drug Administration (FDA) approval of zolpidem extended-release was based on two placebo-controlled trials of three weeks duration. Zolpidem extended-release is indicated for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance.[2]

There are also no published head-to-head trials comparing ramelteon to the other NBRAs, benzodiazepines, or trazodone. One published placebo-controlled crossover trial lasting two nights provides indirect evidence that ramelteon is similar to zolpidem and eszopiclone for objective sleep latency.[13]

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Zolpimist is an oral spray formulation of zolpidem. A single-dose cross over study demonstrated that Zolpimist is bioequivalent to Ambien tablets.[7] Edluar, a sublingual formulation of zolpidem, has demonstrated in a small (N=21) comparison study a significant earlier sleep initiation as compared to an equivalent dose of oral zolpidem in healthy volunteers (12.8 +/- 9.9 minutes versus 18.4 +/- 11.3 minutes, respectively; $p<0.5$).[17] No treatment effects could be evidenced on total sleep time, time awake after sleep onset, or sleep architecture parameters for sublingual zolpidem compared to oral zolpidem.[17]

All of the newer insomnia agents, with the exception of ramelteon, are considered controlled substances and in general should be limited to seven to ten days of use with reevaluation of the patient if they are to be taken for more than two to three weeks.[1-4,6-7] Sleep disturbances may be the presenting symptom of a physical and/or psychiatric disorder and failure to resolve the insomnia with treatment after seven to ten days may indicate the presence of a primary psychiatric and/or mental illness that should be evaluated.[1-4,6-7] Studies of abuse potential in former drug abusers indicate that the effects of single doses of zolpidem 40 mg were similar, but not identical, to diazepam 20 mg, whereas the effects of zolpidem 20 mg were difficult to distinguish from placebo.[1,7] Eszopiclone at doses of 6 mg and 12 mg in patients with histories of benzodiazepine abuse, resulted in euphoric effects similar to diazepam 20 mg.[4] In two studies assessing the abuse potential of zaleplon at 25 mg, 50 mg, and 75 mg in patients with histories of sedative drug abuse indicate an abuse potential similar to benzodiazepines and other NBRAs.[5] A 2005 National Institutes of Health Conference Statement on the management of chronic insomnia concluded that tolerance and abuse of the NBRAs were not major problems in the general population with chronic insomnia but long-term use needed further study.[8].

Ramelteon has a different mechanism of action and is not expected to have the potential for abuse and dependence that the NBRAs share. A double-blind crossover study enrolling fourteen patients with histories of sedative abuse evaluated the potential for abuse of ramelteon compared to triazolam.[18] In this 18-day study, ramelteon demonstrated no significant effects indicating a potential for abuse or motor or cognitive impairment at up to 20 times the recommended therapeutic dose. [18] The use of brand ramelteon may be allowed through the manual PA process if there are concerns about chemical or substance abuse.

ELECTRONIC EDITS

The overall process for step therapy requires that another drug or drugs be tried in a specific previous time period before the claim drug. The program may be implemented with one of two options; 1) a one-step edit that requires therapy with a generic insomnia agent before any brand or 2) a two-step edit that requires use of a generic insomnia agent before use of a preferred brand agent and therapy with both a generic and a preferred brand insomnia agent when a nonpreferred brand is requested.

Claims for a brand NBRA or Rozerem will also automatically pay if the patient's medication history contains evidence of the same brand NBRA or Rozerem within 90 days prior to the new claim. The claims system is designed to identify any claim with a days supply that ends within the 90-day look-back timeframe. Approval of these agents if previous use is identified assures no disruption of therapy for those patients already stabilized on the medication. The 90-day search period was chosen to capture the most current therapy.

If the patient has met any of the requirements outlined below, the requested step therapy medication will be paid under the patient's current prescription benefit.

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Table 1: Summary of Insomnia Step Therapy

Targeted Agent(s)	GPIs	Prerequisite(s)	GPIs	Prerequisite Lookback Time Frame
Option 1 – One Step – Generic First				
ALL brand NBRAs and Rozerem	602040********, 602500********, multisource code M, N, or O	Any generic NBRA	602040******** multisource code Y	90 days[a]
Option 2 - Two Step - Generic before Preferred Brand; - Generic AND Preferred Brand before Nonpreferred brand				
Preferred brand	Determined by client: 602040********, 602500********, multisource code M, N, or O set up at drug or GPI 10 level	Any generic NBRA	602040******** multisource code Y	90 days[a]
Nonpreferred brand	Determined by client: 602040********, 602500********, multisource code M, N, or O set up at drug or GPI 10 level	Any generic NBRA **AND** Any preferred brand, determined by client	602040******** multisource code Y **AND** 602040******** or 602500********, multisource code M, N, or O set up at drug or GPI 10 level	180 days[b]
Is auto-grandfathering implemented? (with look-back time frame)			Yes - 90 days[a] look-back time frame	
Prerequisite look-back time frame for **1** prerequisite (1-step option or *preferred* brand in 2-step option)			90 days[a]	
Number of prerequisites required (*nonpreferred* brand in 2-step option)			2	
Prerequisite look-back time frame for **2** prerequisites (*nonpreferred* brand in 2-step option)			180 days[b]	

a - 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.
b - The system searches for a claim with a days supply that begins or ends in the past 180 days. For claims with a 30 day supply the system would be able to identify a claim processed for payment between 1 and 210 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 270 days.

If the patient does not meet the step therapy criteria, then the system will reject with the message indicating that prior authorization is necessary. The *Prior Authorization (PA) Criteria for Approval* would then be applied to requests submitted by the patient's practitioner for evaluation.

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

The intent of the *Prior Authorization (PA) Criteria for Approval* is to provide a manual review process for claims that do not meet the electronic edit criteria and are not automatically paid. The criteria for approval through the PA process are identical to those set up in the electronic edit.

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The intent of the *PA Criteria for Approval* for step therapy is to allow for approval of brand insomnia agents under step therapy option 1 when the patient's medication history indicates prior use of a generic NBRA not identified by the electronic claims history edit. The PA criteria also allows for use of brand agents if the patient has allergies, intolerance, or contraindication to the use of generic insomnia agents.

The PA Criteria for Approval for step therapy implementing option 2 allows approval of preferred brand agents when the patient's medication history indicates prior a generic NBRA not identified by the electronic claims history, or if the patient has allergies, intolerance, or contraindication to the use of a generic insomnia agent. The PA Criteria for Approval for step therapy option 2 also allows approval of nonpreferred brand agents when there is claims history evidence or medical history evidence that both generic NBRA and a preferred insomnia agent has been previously tried. The PA criteria also allows for use of nonpreferred brand agents if the patient has allergies, intolerance, or contraindication to the use of generic a NBRA or preferred brand insomnia agents. The PA length of approval has been set at twelve months to allow for changes in preferred and nonpreferred formulary status.

In either option, brand NBRAs (preferred or nonpreferred) or Rozerem will also be approved if the patient is previously stabilized on the same brand.

Step Therapy PA Criteria for Approval

Option 1: Brand Insomnia Agents

Initial and Renewal Evaluation

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

2. Is there evidence of prior generic NBRA use in the patient's medication history?
   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?
   If yes, approve for 12 months. If no, deny.

Option 2: Preferred and Nonpreferred Brand Insomnia Agents

Initial and Renewal Evaluation

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

2. Is there evidence of prior generic NBRA therapy in the patient's medication history?
   If yes, continue to 4. If no, continue to 3.

3. Does the patient have an allergy, intolerance, contraindication, or treatment failure to generic NBRA therapy?
   If yes, continue to 4. If no, continue to76.

4. Is the requested brand agent a preferred agent for the patient's plan?
   If yes, approve for 12 months. If no, continue to 5.

5. Is there evidence of prior use of a preferred brand agent in the patient's medication history?
   If yes, approve for 12 months. If no, continue to 6.

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6. Does the patient have an allergy, intolerance, contraindication, or treatment failure to the preferred brand(s)?
   If yes, approve for 12 months. If no, continue to 7.

7. Does the patient require a noncontrolled agent for the treatment of insomnia?
   If yes, continue to 8. If no, deny.

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

SUMMARY

The intent of the step therapy criteria for the nonbenzodiazepine benzodiazepine receptor agonists (NBRAs), (Ambien, Ambien CR, Edluar, Lunesta, Sonata, and Zolpimist), and the melatonin receptor agonist Rozerem, is to encourage the use of the more cost-effective generic agents prior to use of the brand agents. The program has been developed with the opportunity to implement one of two options; 1) a one-step edit that requires therapy with a generic insomnia agent before any brand or 2) a two-step edit that requires use of a generic insomnia agent before use of a preferred brand agent and therapy with both a generic and a preferred brand insomnia agent when a nonpreferred brand is requested. If the patient cannot be treated with a controlled substance Rozerem may be approved for use.

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