Insomnia Agents Step Therapy and Quantity Limit Program Summary

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[1-10]

Agent	Indication[a]	Dosing and Administration
Ambien® (zolpidem)[bc] tablets	Short-term treatment of insomnia characterized by difficulties with sleep initiation Shown 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	Maximum daily dose is 10 mg. Use the lowest effective dose. Recommended doses below: **Women:** 5 mg once daily immediately before bedtime. May increase to 10 mg if needed[d] **Men:** 5 mg provides sufficient efficacy for many men. May increase to 10 mg if needed[d] **Elderly, debilitated, or hepatically impaired patients:** 5 mg once daily
Ambien CR® (zolpidem CR)[bc] tablets	Treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance Clinical trials performed in support of efficacy were up to 3 weeks & 24 wks in duration	Maximum daily dose is 12.5 mg. Use the lowest effective dose. Recommended doses below: **Women:** 6.25 mg once daily immediately before bedtime. May increase to 12.5 mg if needed[d] **Men:** 6.25 mg provides sufficient efficacy for many men. May increase to 12.5 mg if needed[d] **Elderly, debilitated, or hepatically impaired patients**: 6.25 mg once daily
Belsomra® (suvorexant) tablets	Treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance	Recommended dose is 10 mg, no more than once per night taken within 30 minutes of going to bed, with at least 7 hours remaining before the planned time of awakening. If the 10 mg dose is well tolerated but not effective, the dose can be increased, not to exceed 20 mg once daily

Agent	Indication[a]	Dosing and Administration
Edluar® (zolpidem)[b] sublingual tablets	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	Maximum daily dose is 10 mg. Use the lowest effective dose. Recommended doses below: **Women:** 5 mg once daily immediately before bedtime. May increase to 10 mg if needed. [d] **Men:** 5 mg provides sufficient efficacy for many men. May increase to 10 mg if needed. [d] **Elderly, debilitated, or hepatically impaired patients**: 5 mg
Intermezzo® (zolpidem)[bc] 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 Clinical trials supporting efficacy was shown in two clinical trials: Sleep Laboratory Study (3-period crossover) and an Outpatient Study (double blind placebo controlled 4 weeks).	1.75mg for women and 3.5mg for men, taken only once per night as needed. Geriatric patients and patients with hepatic impairment: 1.75 mg once nightly
Lunesta® (eszopiclone)[bc] tablet	Treatment of insomnia 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.	1 mg immediately before bedtime. May increase to maximum of 3 mg if needed. Geriatric or debilitated patients: Maximum 2 mg daily Severe hepatic impairment or on CYP3A4 inhibitors: Maximum 2 mg daily
Rozerem® (ramelteon) tablet	Treatment of 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.	8 mg taken within 30 minutes of going to bed Total Rozerem dose should not exceed 8 mg per day
Silenor® (doxepin) tablet	Treatment of insomnia characterized by difficulty with sleep maintenance The clinical trials performed in support of efficacy were up to 3 months in duration.	6 mg once daily Total daily dose should not exceed 6mg Elderly:3 mg once daily
Sonata® (zaleplon)[bc] capsule	Short-term treatment of insomnia 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.	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)
Zolpimist™	Short-term treatment of insomnia characterized	Maximum daily dose is 10 mg.

Agent	Indication[a]	Dosing and Administration
(zolpidem)[b] oral spray	by difficulties with sleep initiation 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.	Use the lowest effective dose. Recommended doses below: **Women:** 5 mg once daily immediately before bedtime. May increase to 10 mg if needed. [d] **Men:** 5 mg provides sufficient efficacy for many men. May increase to 10 mg if needed. [d] **Elderly, debilitated, or hepatically impaired patients**: 5 mg

a – 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.
b – Hypnotics classified as Schedule IV controlled substances
c – Generics available
d - Compared to lower doses, zolpidem 10 mg (immediate release) or 12.5 mg (extended release) is more likely to impair next-morning activities requiring alertness (e.g., driving).

CLINICAL RATIONALE

Cognitive behavioral therapy (CBT) is the first line treatment for chronic insomnia.[11,14] This treatment comprises advice on sleep-wake behavior (sleep hygiene), stimulus control and sleep restriction, and relaxation and cognitive techniques. Efficacy of CBT has been shown to be equal to pharmacotherapy during acute treatment and more effective for long term treatment.[11,13] Evidence is insufficient to evaluate the balance of the benefits and harms of long-term use of pharmacologic treatments in adults with chronic insomnia disorder.[12]

For patients with sleep onset insomnia, a short-acting medication is a reasonable choice for an initial trial of pharmacologic therapy. This may improve the insomnia with less residual somnolence the following morning. Examples of short-acting medications (duration of effect ≤8 hours) include zaleplon, zolpidem, triazolam, lorazepam, and ramelteon. For patients with sleep maintenance insomnia, a longer-acting medication is preferable for an initial trial of pharmacologic therapy. Examples of longer-acting medications include zolpidem extended release, eszopiclone, temazepam, estazolam, low dose doxepin, and suvorexant. However, these medications may increase the risk for hangover sedation and patients must be warned about this possibility. For patients with awakening in the middle of the night, both zaleplon and a specific sublingual tablet form of zolpidem have been developed for use during the night, with the constraint that there will be at least four hours of time in bed remaining after administration.[13]

All insomnia drugs can impair activities requiring alertness (e.g., driving) the morning after use. Patients can experience impairment of mental alertness the morning after use, even if they feel fully awake. Women appear more susceptible to this risk due to slower elimination of zolpidem vs men.[15]

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.[16] Benzodiazepine-receptor agonists have adverse events similar to those of benzodiazepines in older adults (e.g., delirium, falls, fractures); increased emergency department 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.[16]

For additional clinical information see Prime Therapeutics Formulary Chapters 9.4D: Hypnotics: Non-Benzodiazepine GABA-Receptor Modulators; and 9.4E: Selective Melatonin Receptor Agonist.

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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 hypnotics (Ambien, Ambien CR, Belsomra, Edluar, Lunesta, Sonata, and Zolpimist), melatonin receptor agonist (Rozerem), and histamine H_1 receptor antagonist (Silenor) when generic agents cannot be used due to documented intolerance, FDA labeled contraindication, or hypersensitivity. All dosage forms of the brand agents listed will be included as targets in the step therapy program. If the patient cannot be treated with a controlled substance, Rozerem or Silenor may be approved for use.

TARGET AGENTS
Ambien® (zolpidem)[a]
Ambien CR® (zolpidem)[a]
Belsomra® (suvorexant)
Edluar® (zolpidem)
Intermezzo® (zolpidem)[a]
Lunesta® (eszopiclone)[a]
Rozerem® (ramelteon)
Silenor® (doxepin)
Sonata® (zaleplon)[a]
Zolpimist™ (zolpidem)
a – generic available that is a prerequisite agent for step therapy program

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Brand Insomnia Agents will be approved when ONE of the following is met:
1. The patient's medication history includes the use of a generic nonbenzodiazepine hypnotic agent in the past 90 days
   OR
2. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to the available generic nonbenzodiazepine hypnotic agents
   OR
3. The patient requires therapy with the non-controlled agent, Rozerem or Silenor

Length of Approval: 12 months

NOTE: If Quantity Limit program also applies, please refer to Quantity Limit documents.

Step Therapy Supplement

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

Please note, this does not include or apply to quantity limit questions.

STEP THERAPY SUPPLEMENT
OBJECTIVE
The intent of the Step Therapy Supplement is to provide additional questions, to ensure compliance to MN Statute 62Q.184. These questions will apply if the step therapy component within a Prior Authorization or Step Therapy program is not able to be approved.

CONDITIONS FOR APPROVAL
The requested agent will be approved when ONE of the following are 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
    AND
    b. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
    AND
    c. The prescriber states that a change in therapy is expected to be ineffective or cause harm

    OR
2. The patient's medication history include the required prerequisite/preferred agent(s) as indicated by:
    a. Evidence of a paid claim(s) within the past 999 days
    OR
    b. The prescriber has stated that the patient has tried the required prerequisite/preferred agent(s) in the past 999 days AND the required prerequisite/preferred agent(s) was discontinued due to lack of effectiveness or an adverse event

    OR
3. The prescriber has provided documentation that the required prerequisite/preferred agent(s) 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

Length of Approval: As per program specific criteria