Insomnia Agents Step Therapy with Quantity Limit Program Summary

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

POLICY REVIEW CYCLE

Effective Date **Date of Origin**
07-01-2024

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
AMBIEN® (zolpidem)*^ Tablet	Short-term treatment of insomnia characterized by difficulties with sleep initiation	*Hypnotics classified as Schedule IV controlled substances ^generic available	2
AMBIEN CR® (zolpidem CR)*^ Tablet	Short-term treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance	*Hypnotics classified as Schedule IV controlled substances ^generic available	1
Belsomra® (suvorexant)* Tablet	Treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance	*Hypnotics classified as Schedule IV controlled substances	3
DAYVIGO® (lemborexant)* Tablet	Treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance	*Hypnotics classified as Schedule IV controlled substances	13
EDLUAR® (zolpidem)* Sublingual tablet	Short-term treatment of insomnia characterized by difficulties with sleep initiation	*Hypnotics classified as Schedule IV controlled substances	4
Lunesta® (eszopiclone)*^	Treatment of insomnia	*Hypnotics classified as Schedule IV controlled substances	6

Agent(s)	FDA Indication(s)	Notes	Ref#
Tablet		^generic available	
QUVIVIQ® (daridorexant)* Tablet	Treatment of adult patients with insomnia characterized by difficulties with sleep onset and/or sleep maintenance	*Hypnotics classified as Schedule IV controlled substances	14
Rozerem® (ramelteon)^ Tablet	Treatment of insomnia characterized by difficulty with sleep onset	^generic available	7
Silenor® (doxepin)^ Tablet	Treatment of insomnia characterized by difficulty with sleep maintenance	^generic available	8
Zolpidem Tartrate* Capsule	Short-term treatment of transient insomnia characterized by difficulties with sleep initiation in adults younger than age 65 years of age	*Hypnotics classified as Schedule IV controlled substances	16
Zolpidem Sublingual tablet	Treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep	*Hypnotics classified as Schedule IV controlled substances	5
ZolpiMist (zolpidem)* Oral spray	Short-term treatment of insomnia characterized by difficulties with sleep initiation	*Hypnotics classified as Schedule IV controlled substances	9

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Insomnia	Insomnia is the most prevalent sleep disorder and can be associated with numerous adverse effects on function, health, and quality of life. (10,11) The American Academy of Sleep Medicine and the American College of Physicians created clinical guidelines for the management (psychological/behavioral and pharmacological).(10,11,15) The guidelines indicate psychological/behavioral interventions are first line and as effective as pharmacologic therapies. Initial approaches to treatment should include at least one behavioral intervention such as stimulus control therapy or relaxation therapy, or the combination of cognitive therapy, stimulus control therapy, sleep restriction therapy with or without relaxation therapy, otherwise known as cognitive behavioral therapy for insomnia (CBT-I). Short-term hypnotic therapy should be supplemented with behavioral and cognitive therapies.(10,15) The guidelines recommend these general sequence of medication trials for patients with primary insomnia:(15)

	• 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:(15) • 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. Over-the-counter antihistamine or antihistamine/analgesic type drugs (OTC "sleep aids") as well as herbal and nutritional substances (e.g., valerian and melatonin) are not recommended in the treatment of chronic insomnia due to the relative lack of efficacy and safety data.(15)
Safety	AMBIEN, AMBIEN CR, EDLUAR, Zolpidem sublingual tablet, Zolpidem capsule, and ZolpiMist have boxed warnings regarding complex sleep behaviors:(1,2,4,5,9,16) Complex sleep behaviors including sleep-walking, sleep-driving, and engaging in other activities while not fully awake may occur following use of AMBIEN, AMBIEN CR, EDLUAR, Zolpidem sublingual tablet, Zolpidem capsule, and ZolpiMist. Some of these events may result in serious injuries, including death. Discontinue AMBIEN, AMBIEN CR, EDLUAR, Zolpidem sublingual tablet, Zolpidem capsule, and ZolpiMist immediately if a patient experiences a complex sleep behavior. AMBIEN, AMBIEN CR, EDLUAR, Zolpidem sublingual tablet, Zolpidem capsule, and ZolpiMist are contraindicated in the following: (1,2,4,5,9,16) • Patient who have experienced complex sleep behaviors taking zolpidem

	• Known hypersensitivity to zolpidem Belsomra, DAYVIGO, and QUVIVIQ are contraindicated in patients with narcolepsy.(3,13,14) Lunesta is contraindicated in the following:(6) • Patient who have experienced complex sleep behaviors taking eszopiclone • Known hypersensitivity to eszopiclone Rozerem is contraindicated in the following:(7) • Patient who develop angioedema after treatment with ramelteon • In combination with fluvoxamine Silenor is contraindication in the following:(8) • Known hypersensitivity to doxepin, any of the inactive ingredients, or other dibenzoxepines • Coadministration or use within the past 14 days with a monoamine oxidase inhibitor (MAOI) • In patients with untreated narrow angle glaucoma or severe urinary retention
Use in the Elderly	Every three years, the American Geriatrics Society (AGS) revises the list of Potentially Inappropriate Medications for use in individuals over the age of 65, which is known as the Beers Criteria. The Beers Criteria provides recommendations for medications that should be avoided in this population.(12) Zolpidem, zaleplon, and eszopiclone are all included in the Beers Criteria. Benzodiazepine-receptor agonist hypnotics (i.e., Z drugs) have adverse events similar to 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 eszopiclone, zaleplon, and zolpidem drugs be avoided in persons over the age of 65.(12) Doxepin doses that are less than or equal to 6 mg have demonstrated side effect profile that are similar to a placebo. But doses greater 6 mg have been found to be highly anticholinergic and associated with orthostatic hypotension and increased sedation. Based on the side effect profile, the AGS recommends that doxepin doses greater than 6 mg should be avoided in persons over the age of 65.(12)

REFERENCES

Number	Reference
1	AMBIEN CR prescribing information. Sanofi-Aventis U.S. LLC. February 2022.
2	AMBIEN prescribing information. Sanofi-Aventis U.S. LLC. February 2022.
3	Belsomra prescribing information. Merck Sharp & Dohme LLC. February 2023.
4	EDLUAR prescribing information. Meda Pharmaceuticals Inc. August 2022.
5	Zolpidem sublingual tablet prescribing information. Par Pharmaceuticals. October 2019.
6	Lunesta prescribing information. Sunovian Pharmaceuticals, Inc. August 2019.
7	Rozerem prescribing information. Takeda Pharmaceuticals America, Inc. November 2021.
8	Silenor prescribing information. Currax Pharmaceuticals LLC. December 2022.
9	ZolpiMist prescribing information. Magna Pharmaceuticals. August 2019.

Number	Reference
10	Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD, for the Clinical Guidelines Committee of the American College of Physicians. Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med. 2016;165:125-133. doi: 10.7326/M15-2175
11	Sateia, Michael J, MD, et al. Clinical Practice Guidelines for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. *Journal of Clinical Sleep Medicine*. 2017. 13 (2): 307-349.
12	By the 2023 American Geriatrics Society Beers Criteria® Update Expert Panel (2023). American Geriatrics Society 2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. Journal of the American Geriatrics Society, 71(7), 2052-2081. https://doi.org/10.1111/jgs.18372
13	DAYVIGO prescribing information. Eisai Inc. June 2022.
14	QUVIVIQ prescribing information. Idorsia Pharmaceuticals LTD. October 2023.
15	Schutte-Rodin S, Broch L, Buysse D, et al. Clinical guideline for the evaluation and management of chronic insomnia in adults. J Clin Sleep Med. 2008;4(5): 487-504.
16	Zolpidem Tartrate Capsules prescribing information. Almatica Pharma LLC. May 2023

POLICY AGENT SUMMARY STEP THERAPY

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
	zaleplon cap	10 MG ; 5 MG	M ; N ; O	Y		
Ambien ; Ambien cr ; Edluar ; Zolpimist	zolpidem tartrate cap ; zolpidem tartrate oral spray ; zolpidem tartrate sl tab ; zolpidem tartrate tab ; zolpidem tartrate tab er	1.75 MG ; 10 MG ; 12.5 MG ; 3.5 MG ; 5 MG ; 5 MG/ACT ; 6.25 MG ; 7.5 MG	M ; N ; O	N ; O ; Y		
Belsomra ; Dayvigo ; Quviviq	daridorexant hcl tab ; lemborexant tab ; suvorexant tab	10 MG ; 15 MG ; 20 MG ; 25 MG ; 5 MG ; 50 MG	M ; N ; O	N		
Lunesta	eszopiclone tab	1 MG ; 2 MG ; 3 MG	M ; N ; O	O ; Y		
Rozerem	ramelteon tab	8 MG	M ; N ; O	O ; Y		
Silenor	doxepin hcl (sleep) tab	3 MG ; 6 MG	M ; N ; O	O ; Y		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
	zaleplon cap	10 MG ; 5 MG	30	Capsules	30	DAYS			
	zolpidem tartrate cap	7.5 MG	30	Capsules	30	DAYS			
Ambien	zolpidem tartrate tab	10 MG ; 5 MG	30	Tablets	30	DAYS			

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Ambien ; Ambien cr ; Edluar ; Zolpimist	zolpidem tartrate cap ; zolpidem tartrate oral spray ; zolpidem tartrate sl tab ; zolpidem tartrate tab ; zolpidem tartrate tab er	1.75 MG ; 10 MG ; 12.5 MG ; 3.5 MG ; 5 MG ; 5 MG/ACT ; 6.25 MG ; 7.5 MG	30	Tablets	30	DAYS			
Ambien cr	zolpidem tartrate tab er	12.5 MG ; 6.25 MG	30	Tablets	30	DAYS			
Belsomra ; Dayvigo ; Quviviq	daridorexant hcl tab ; lemborexant tab ; suvorexant tab	10 MG ; 15 MG ; 20 MG ; 25 MG ; 5 MG ; 50 MG	30	Tablets	30	DAYS			
Edluar	zolpidem tartrate sl tab	1.75 MG ; 10 MG ; 3.5 MG ; 5 MG	30	Tablets	30	DAYS			
Lunesta	eszopiclone tab	1 MG ; 2 MG ; 3 MG	30	Tablets	30	DAYS			
Rozerem	ramelteon tab	8 MG	30	Tablets	30	DAYS			
Silenor	doxepin hcl (sleep) tab	3 MG ; 6 MG	30	Tablets	30	DAYS			
Zolpimist	Zolpidem Tartrate Oral Spray 5 MG/ACT	5 MG/ACT	1	Canister	30	DAYS			

CLIENT SUMMARY – STEP THERAPY

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
	zaleplon cap	10 MG ; 5 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; KeyRx
Ambien ; Ambien cr ; Edluar ; Zolpimist	zolpidem tartrate cap ; zolpidem tartrate oral spray ; zolpidem tartrate sl tab ; zolpidem tartrate tab ; zolpidem tartrate tab er	1.75 MG ; 10 MG ; 12.5 MG ; 3.5 MG ; 5 MG ; 5 MG/ACT ; 6.25 MG ; 7.5 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; KeyRx
Belsomra ; Dayvigo ; Quviviq	daridorexant hcl tab ; lemborexant tab ; suvorexant tab	10 MG ; 15 MG ; 20 MG ; 25 MG ; 5 MG ; 50 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; KeyRx
Lunesta	eszopiclone tab	1 MG ; 2 MG ; 3 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; KeyRx
Rozerem	ramelteon tab	8 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; KeyRx
Silenor	doxepin hcl (sleep) tab	3 MG ; 6 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; KeyRx

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
	zaleplon cap	10 MG ; 5 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
	zolpidem tartrate cap	7.5 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Ambien	zolpidem tartrate tab	10 MG ; 5 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Ambien ; Ambien cr ; Edluar ; Zolpimist	zolpidem tartrate cap ; zolpidem tartrate oral spray ; zolpidem tartrate sl tab ; zolpidem tartrate tab ; zolpidem tartrate tab er	1.75 MG ; 10 MG ; 12.5 MG ; 3.5 MG ; 5 MG ; 5 MG/ACT ; 6.25 MG ; 7.5 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Ambien cr	zolpidem tartrate tab er	12.5 MG ; 6.25 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Belsomra ; Dayvigo ; Quviviq	daridorexant hcl tab ; lemborexant tab ; suvorexant tab	10 MG ; 15 MG ; 20 MG ; 25 MG ; 5 MG ; 50 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Edluar	zolpidem tartrate sl tab	1.75 MG ; 10 MG ; 3.5 MG ; 5 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Lunesta	eszopiclone tab	1 MG ; 2 MG ; 3 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Rozerem	ramelteon tab	8 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Silenor	doxepin hcl (sleep) tab	3 MG ; 6 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Zolpimist	Zolpidem Tartrate Oral Spray 5 MG/ACT	5 MG/ACT	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

STEP THERAPY CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval

TARGET AGENT(S)	PREREQUISITE AGENT(S)
Ambien (zolpidem)* **Ambien CR** (zolpidem)* **Belsomra** (suvorexant) **Dayvigo** (lemborexant) **Edluar** (zolpidem) **Lunesta** (eszopiclone)* **Quviviq** (daridorexant) **Rozerem** (ramelteon)^ **Silenor** (doxepin)^ **Zolpidem sublingual tablet**+ **Zolpidem tartrate capsule**+ **ZolpiMist** (zolpidem)	zolpidem eszopiclone zaleplon

* – generic available that is a prerequisite agent for step therapy program
^ – generic available
+ – branded generic product(s) available; targeted in the step therapy program

Brand Insomnia Agent(s) 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 (starting on samples is not approvable) **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 includes the use of a prerequisite agent **OR**
3. BOTH of the following:
   A. The prescriber has stated that the patient has tried a prerequisite agent **AND**
   B. Prerequisite agent was discontinued due to lack of effectiveness or an adverse event **OR**
4. The patient has an intolerance or hypersensitivity to prerequisite agents **OR**
5. The patient has an FDA labeled contraindication to ALL prerequisite agents **OR**
6. The prescriber has provided documentation that ALL prerequisite 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 **OR**
7. 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 applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval

Quantity limit for the Target Agent(s) will be approved when ONE of the following is met:

1. The requested quantity (dose) does NOT exceed the program quantity limit **OR**
2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following:
   A. BOTH of the following:
      1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND**
      2. There is support for therapy with a higher dose for the requested indication **OR**
   B. BOTH of the following:
      1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND**

Module	Clinical Criteria for Approval
	2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months