# Pharmacy Policy Bulletin

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| **Title:** | Sleep Agents |
| **Policy #:** | Rx.01.84 |

***Application of pharmacy policy is determined by benefits and contracts. Benefits may vary based on product line, group, or contract. Some medications may be subject to precertification, age, quantity, or formulary restrictions (ie limits on non-preferred drugs). Individual member benefits must be verified.***

***This pharmacy policy document describes the status of pharmaceutical information and/or technology at the time the document was developed. Since that time, new information relating to drug efficacy, interactions, contraindications, dosage, administration routes, safety, or FDA approval may have changed. This Pharmacy Policy will be regularly updated as scientific and medical literature becomes available. This information may include new FDA-approved indications, withdrawals, or other FDA alerts. This type of information is relevant not only when considering whether this policy should be updated, but also when applying it to current requests for coverage.***

***Members are advised to use participating pharmacies in order to receive the highest level of benefits.***

**Intent:**

The intent of this policy is to communicate the medical necessity criteria for **zolpidem tartrate (Ambien® and Ambien CR®), zolpidem (Intermezzo®, Zolpimist®), zolpidem tartrate sublingual tablets (Edluar®), eszopiclone 3mg (Lunesta®) and tasimelteon (Hetlioz®/Hetlioz LQ®)** as provided under the member's prescription drug benefit.

**Description:**

Insomnia is one of the most common medical complaints, generating more than 5 million office visits per year in the United States. Typical complaints include difficulty falling asleep, staying asleep, and variable sleep. Insomnia is present when all of the following criteria are met:

1. A complaint of difficulty initiating sleep, difficulty maintaining sleep, or waking up too early. In children or individuals with dementia, the sleep disturbance may manifest as resistance to going to bed at the appropriate time or difficulty in sleeping without caregiver assistance.
2. The above sleep difficulty occurs despite adequate opportunity and circumstances for sleep.
3. The impaired sleep produces deficits in daytime function.

Insomnia is classified as short-term, long-term, or other depending upon the duration and causes.

Non-24-hour sleep-wake rhythm disorder is characterized by failure of the circadian system to maintain stable alignment (called "entrainment") to the 24-hour day. As a result, the circadian system "free runs" and typically shifts to progressively later phase positions. The most common cause is blindness, as the daily light-dark cycle is the most powerful environmental cue for synchronizing the hypothalamic pacemaker to the 24-hour day.

Sleep problems are often significant in individuals diagnosed with Smith-Magenis Syndrome and include difficulty falling asleep, shortened sleep cycles, frequent and prolonged nocturnal awakening (altered rapid eye movement [REM] sleep), excessive daytime sleepiness, daytime napping, snoring, and bedwetting. Sleep problem appear to be due to an inversion of melatonin secretion.

Zolpidem tartrate (Ambien®) is a gamma-aminobutyric acid (GABA) A receptor positive modulator, is indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation.

Zolpidem tartrate (Ambien CR®) is a gamma-aminobutyric acid (GABA) A receptor positive modulator, is indicated for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance.

Zolpidem tartrate (Edluar®) and (Zolpimist®) are gamma-aminobutyric acid (GABA) A receptor positive modulators indicated for the treatment of insomnia characterized by difficulties with sleep initiation.

Zolpidem tartrate sublingual tablet (Intermezzo®) is a $GABA_A$ agonist indicated for use as needed for the treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep.

Zolpidem tartrate sublingual tablet (Intermezzo®) is a $GABA_A$ agonist indicated for use as needed for the treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep.

Tasimelteon (Hetlioz®/ Hetlioz LQ®) is indicated for:

1. Capsules: Treatment of non-24-Hour Sleep-Wake Disorder (Non-24) in adults and nighttime sleep disturbances in Smith-Magenis Syndrome (SMS) in patients 16 years of age and older
2. Oral suspension: Treatment of nighttime sleep disturbances in SMS in pediatric patients 3 years to 15 years of age

Tasimelteon (Hetlioz®/ Hetlioz LQ®) is an agonist of melatonin receptors $MT_1$ and $MT_2$ (greater affinity for the $MT_2$ receptor than the $MT_1$ receptor). Activation of $MT_1$ is thought to preferentially induce sleepiness, while $MT_2$ receptor activation preferentially influences regulation of circadian rhythms.

**Policy:**

***Insomnia***

**INITIAL CRITERIA:** Edluar® 5mg, Zolpimist®, Intermezzo® 1.75mg are approved when ALL of the following are met:

1. Diagnosis of insomnia; and
2. Member is 18 years of age or older; and
3. One of the following:
    a. Inadequate response or inability to tolerate TWO of the following:
        i. Eszopiclone
        ii. Zaleplon
        iii. Zolpidem; OR
    b. Inability to swallow capsules/tablets (i.e., dysphagia, gastrointestinal [GI] tubes)

**INITIAL CRITERIA:** Any of the following high dose products (brand and generic): zolpidem tartrate (Ambien®) 10mg, zolpidem tartrate ER (Ambien® CR) 12.5mg, zolpidem tartrate SL (Intermezzo®) 3.5mg, eszopiclone (Lunesta®) 3mg or Edluar® 10mg is approved when ALL of the following are met:

1. Diagnosis of insomnia; and
2. Member is 18 years of age or older; and
3. Patient has been counseled on practices associated with good sleep hygiene (e.g. avoiding stimulants such as caffeine, nicotine, alcohol close to bed time, etc.); and
4. Inadequate response to a two-week trial of the lower dose; and
5. For brand products with generic equivalents only, inadequate response or inability to tolerate a generic equivalent

Initial authorization duration: 2 years

**REAUTHORIZATION CRITERIA:** Edluar® 5mg, Zolpimist®, Intermezzo® 1.75mg, zolpidem tartrate (Ambien®) 10mg, zolpidem tartrate ER (Ambien® CR) 12.5mg, zolpidem tartrate SL (Intermezzo®) 3.5mg, eszopiclone (Lunesta®) 3mg, or Edluar® 10mg is re-approved when there is documentation of positive clinical response to therapy.

Reauthorization duration: 2years

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***Non-24-hour sleep Sleep-Wake Disorder***

**INITIAL CRITERIA:** Tasimelteon (Hetlioz®/Hetlioz LQ®) is approved when ALL of the following are met:

1. Prescribed by or in consultation with a sleep specialist; and
2. Diagnosis of Non-24-hour sleep Sleep-Wake Disorder; and
3. Member is 18 years of age or older; and
4. Member is totally blind; and

5. Member has circadian period greater than 24 hours; and
6. Inadequate response or inability to tolerate ramelteon (Rozerem®)

Initial authorization duration: 2 years

**REAUTHORIZATION CRITERIA:** Hetlioz®/Hetlioz LQ® is re-approved when there is documentation of positive clinical response to therapy.

Reauthorization duration: 2 years

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***Smith-Magenis Syndrome***

**INITIAL CRITERIA:** Tasimelteon (Hetlioz®/Hetlioz LQ®) is approved when ALL of the following are met:

1. Prescribed by or in consultation with a sleep specialist; and
2. Diagnosis of Smith-Magenis Syndrome; and
3. Member experiences nighttime sleep disturbances; and
4. One of the following:
    a. For Hetlioz only, member is 16 years of age or older; or
    b. For Hetlioz LQ only, member is 3 to 15 years of age

Initial authorization duration: 2 years

**REAUTHORIZATION CRITERIA:** Hetlioz®/Hetlioz LQ® is re-approved when there is documentation of positive clinical response to therapy.

Reauthorization duration: 2 years

**Black Box Warning as shown in the drug Prescribing Information:**

Complex Sleep Behaviors: **zolpidem tartrate (Ambien® and Ambien CR®), zolpidem (Intermezzo®, Zolpimist®), zolpidem tartrate sublingual tablets (Edluar®), eszopiclone 3mg (Lunesta®)** Complex sleep behaviors including sleepwalking, sleep driving, and engaging in other activities while not fully awake have been reported following use of zolpidem tartrate and eszopiclone. Some of these events have resulted in serious injuries, including death. Discontinue immediately if a patient experiences a complex sleep behavior.

**Guidelines:**

Refer to the specific manufacturer's prescribing information for administration and dosage details and any applicable Black Box warnings.

**BENEFIT APPLICATION**

Subject to the terms and conditions of the applicable benefit contract, the applicable drug(s) identified in this policy is (are) covered under the prescription drug benefits of the Company's products when the medical necessity criteria listed in this pharmacy policy are met. Any services that are experimental/investigational or cosmetic are benefit contract exclusions for all products of the Company.

**References:**

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Lunesta® (eszopiclone) [prescribing information]. Marlborough, MA: Sunovion Pharmaceuticals Inc. August 2019. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=fd047b2b-05a6-4d99-95cb-955f14bf329f. Accessed April 20, 2023.

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**Applicable Drugs:**

Inclusion of a drug in this table does not imply coverage. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

| Brand Name | Generic Name |
|---|---|
| Ambien® [CR] | zolpidem tartrate immediate and extended release (PA applies to generic 10mg IR and 12.5mg CR) |
| Edluar® | zolpidem sublingual tablets |
| Zolpimist® | zolpidem |
| Intermezzo® | zolpidem |
| Lunesta® | eszopiclone |
| Hetlioz®/Hetlioz LQ® | Tasimelteon |

**Cross References:**

Off-Label Use Rx.01.33

Quantity Level Limits for Pharmaceuticals Covered Under the Prescription Drug Benefit Rx.01.76

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| **Policy Version Number:** | 18.00 |
| **P&T Approval Date:** | March 16, 2023 |
| **Policy Effective Date:** | July 01, 2023 |
| **Next Required Review Date:** | March 16, 2024 |