Sedative and Hypnotic Drug Therapy Policy

**BENEFIT APPLICATION**

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

**DESCRIPTION**

The intent of the sedative and hypnotic drug policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines and clinical studies. Currently in the US, several non-benzodiazepine hypnotics for insomnia are available (e.g. zolpidem, zaleplon, ramelteon, tasimelteon, eszopiclone, and zolpidem CR). With the exception of suvorexant, an orexin receptor antagonist; ramelteon and tasimelteon, dual acting melatonin receptor agonists (MT₁ and MT₂ agonists); and Silenor (doxepin) a tricyclic with a proposed mechanism of action as a H₁ receptor antagonist, the rest of the agents work through gamma-aminobutyric (GABA) receptors. While all of the aforementioned agents are approved for treatment of insomnia, their specific FDA indications are noted below.

**Indication(s):**

- **Belsomra**: For the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.
- **Edluar**: Sublingual formulation for the short-term treatment of insomnia characterized by difficulties with sleep initiation.
- **Hetlioz**: For the treatment of Non-24-Hour Sleep-Wake Disorder (Non-24).
- **Intermezzo**: For use as needed for the treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep.
- **Rozerem**: For the treatment of insomnia characterized by difficulty with sleep onset.
- **Silenor**: For the treatment of insomnia characterized by difficulties with sleep maintenance.
- **Zolpimist**: Oral solution spray for the short-term treatment of insomnia characterized by difficulties with sleep initiation.
I. Hetlioz may be considered medically necessary for the treatment of Non-24-Hour Sleep-Wake Disorder (Non-24) when all of the following criteria are met:
   • Patient is ≥ 18 years of age
   • Patient is totally blind with no visual light perception
   • There is a documented diagnosis of Non 24 sleep-wake disorder by a sleep specialist
   • Patient has tried and failed timed-released melatonin under the direction of a sleep specialist AND has tried and failed Rozerem (ramelteon) unless the patient is currently receiving a positive therapeutic outcome on the requested medications through health insurance (excludes obtainment as samples or via manufacturer’s patient assistance programs)

Approval will be for lifetime

II. Belsomra may be considered medically necessary for the treatment on insomnia when all of the following criteria are met:
   • Patient is ≥ 18 years of age
   • Potential causes of sleep disturbances have been addressed such as sleep hygiene, sleep environment and medical or physiologic causes of chronic insomnia
   • Patient has tried and failed at least TWO of the generically available sedative hypnotics (zolpidem or zolpidem ER, eszopiclone, zaleplon) unless the patient is currently receiving a positive therapeutic outcome on the requested medications through health insurance (excludes obtainment as samples or via manufacturer’s patient assistance programs)
   • The initial starting dose is not greater than 10 mg once nightly

Approval will be for lifetime

III. Silenor and Rozerem may be considered medically necessary for the treatment of insomnia when all the following criteria are met:
   • Patient is > 18 years of age
   • Potential causes of sleep disturbances have been addressed such as sleep hygiene, sleep environment and medical or physiologic causes of chronic insomnia
   • The patient has tried and failed at least TWO of the generically available sedative hypnotics (zolpidem or zolpidem ER, eszopiclone, zaleplon) unless the patient is currently receiving a positive therapeutic outcome on the requested medications through health insurance (excludes obtainment as samples or via manufacturer’s patient assistance programs)

Approval will be for lifetime

IV. Edluar and Zolpimist may be considered medically necessary for the treatment of short term insomnia with difficulty of sleep initiation when all the following criteria are met:
   • Patient is > 18 years of age
   • Potential causes of sleep disturbances have been addressed such as sleep hygiene, sleep environment and medical or physiologic causes of chronic insomnia
   • Patient is unable to swallow capsules/tablets related to a medical condition (including but not limited to: stroke, multiple sclerosis, muscular dystrophy, Parkinson’s disease, scleroderma, diverticula, post-polio syndrome, polymyositis and dermatomyositis.

Approval will be for lifetime
V. Intermezzo may be considered **medically necessary** for the treatment of insomnia when a middle-of-the-night awakening is followed by difficulty in returning to sleep when all of the following criteria are met:
- Patient is ≥ 18 years of age
- Potential causes of sleep disturbances have been addressed such as sleep hygiene, sleep environment and medical or physiologic causes of chronic insomnia
- The initial starting dose of 1.75mg is not exceeded in patients that are female, over age 65 years or taking concomitant CNS depressants such as opioids, benzodiazepines, tricyclics or alcohol

**Approval** will be for **lifetime**

VI. Edluar, Hetlioz, Intermezzo, Rozerem, Zolpimist, and Silenor are considered **not medically necessary** for patients who do not meet the criteria set forth above.

**Quantity limits apply:** Belsomra 30 tablets/30 days, Hetlioz 30 capsules/30 days

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**CLINICAL RATIONALE**

The prevalence of insomnia is estimated to be about 30-50% depending on the methods and definitions used to define the condition. The majority of those (approximately 75%) report insomnia as “occasional” averaging about 6 nights per month. The remaining 25% report frequent or chronic insomnia averaging about 16 nights per month. The risk of sleep disorders increases with age. Patients with insomnia report a combination of falling asleep and intermittent wakefulness during sleep. Consequences of insomnia can include increased risk of depression, poor memory, reduced concentration and poor work performance.

While some individuals may require longer-term treatment, short-term use of insomnia medications is recommended. Published, evidence-based, class reviews of the non-benzodiazepine insomnia medications found limited comparison data hindering the ability to make meaningful comparisons between medications and between specific patient populations. At this time there doesn’t appear to be clinically significant differences between the agents when they are dosed in equipotent doses.

The FDA posted a safety bulletin on 1-10-13 to notify the public in regard to use of zolpidem. The FDA recommends that the bedtime dose be lowered because new data showed that blood levels in some patients may still be high enough in the morning after use to impair activities such as driving that require alertness. This announcement focused on zolpidem products approved for bedtime use generic and brand name products. Brand names included are Ambien, Ambien CR, Edluar and Zolpimist. Most products have adjusted package insert information to reflect these safety concerns.

Zolpidem is available in several formulations, including sublingual tablets an oral spray as well as immediate and controlled-release tablets. Edluar is a sublingual formulation of zolpidem available in 5 mg and 10 mg strengths and Zolpimist is an oral spray formulation that is available in a 5 mg per actuation dose. As immediate-release zolpidem tablets are available in 5 mg and 10mg tablet for the same indication of difficult sleep initiation, Edluar and Zolpimist will be reserved for patients that are unable to swallow capsules/tablet formulations due to a medical condition including but not limited to: stroke, multiple sclerosis, muscular dystrophy, Parkinson’s disease, scleroderma, diverticula, post-polio syndrome, polymyositis and dermatomyositis.

Intermezzo is a sublingual form of zolpidem used for the treatment of middle of the night awakening followed by difficulty in returning to sleep. Intermezzo is not indicated for use when the patient has less than 4 hours of remaining sleep time. The maximum recommended dose is 1.75 mg for women and 3.5 mg for men. These different dosages are recommended because women clear zolpidem from the body at a lower rate...
than men. The recommended dosage for Intermezzo for men and women over the age of 65 years is 1.75mg as well as patients that are taking additional CNS depressants such as benzodiazepines, opioids, tricyclic antidepressants and alcohol.

Hetlioz (tasimelteon) is indicated for the treatment of Non-24 Sleep-Wake Disorder (Non-24), which is a rare, chronic, primary circadian rhythm sleep disorder (CSRD), primarily occurring in patients who are totally blind (have no visual light perception). While most people have a circadian rhythm (or internal body clock) longer than 24 hours, environmental cues, such as light, entrain, or synchronize them, to a 24-hour period. For those who are totally blind without visual light perception this necessary cue is absent, which can lead to the drifting and shifting of sleep times. Hetlioz is currently the only FDA approved product for the treatment of Non-24. Prior to its approval, the provision of care largely involved use of melatonin, which is regulated as a dietary supplement in the US. The American Academy of Sleep Medicine (AASM), in its practice parameter guideline, last updated in 2007, recommends melatonin as treatment for blind patients with Non-24. This recommendation was based on 4 case reports and 5 small studies (e.g. n=7, n=10), with entrainment rates reported between 70% and 86% in the small studies. Overall, based on the results of a poor quality efficacy and safety trial (SET) and a fair quality placebo-controlled withdrawal trial (RESET), the FDA granted approval and orphan drug designation to Hetlioz, indicating the risk-benefit assessment appears favorable for the treatment of Non-24 in the totally blind. Based on the small number of patients included in trials and the significant issues with trial design, it remains unclear as to whether this product has a significant advantage over guideline recommended melatonin, which is also supported by small studies with inherent flaws. Additionally, the disagreement between the sponsor and the FDA on selection of a relevant endpoint for the Hetlioz trials only further magnifies the fact there is no clear cut marker to assess response to treatment, nor equate treatment effect for these endpoints to clinically meaningful health outcomes for patients with Non-24. While Hetlioz is the only FDA approved product for Non-24, it is not the only approved dual acting melatonin receptor. Rozerem (ramelteon), approved for the treatment of insomnia characterized by difficulty with sleep onset, has a similar mechanism of action and pharmacokinetic profile, suggesting it may provide similar benefit at a much lower cost. Rozerem, when taken chronically, costs approximately $3000/year compared to >$84,000 for Hetlioz.

Belsomra offers another mechanism of action for the treatment of insomnia, demonstrating an improvement in both sleep onset and sleep maintenance against placebo in clinical trials. The majority of the data, however, represents higher doses of Belsomra than were FDA approved. For the recommended 10 mg dose, the efficacy data is limited to phase 2 data from 62 patients. The lower doses of Belsomra appear to significantly improve measures of sleep maintenance, but less consistently so for sleep onset. There are currently a variety of sleep agents available generically, representing several mechanisms of action. Comparative efficacy of Belsomra with these agents has not been established; indirect comparisons are difficult due to significant differences in trial design. While offering a new mechanism of action against insomnia, Belsomra does not appear to have advantages from a safety perspective. The higher doses studied were rejected by the FDA due to safety concerns, particularly as Belsomra has a lengthy half-life, dose dependent adverse events, and the potential for factors such as gender, obesity, and concomitant drug use to influence the exposure to the drug. Dose dependent daytime somnolence was the most prominent adverse event. Significant next day driving impairment was demonstrated following both the first dose and after a week of dosing. Case reports of narcolepsy-associated events, unconscious nighttime behaviors and suicidal ideation pose concern. Given generally healthy patients, free of significant psychiatric and medical comorbidity were studied in trials, risk may be greater in the general population, particularly those most likely to use Belsomra. Post-marketing experience will provide a more clear understanding of its safety profile. Due to the potential for abuse, misuse and dependency, Belsomra has been classified as a Scheduled IV controlled substance.

The recommended dosing for Belsomra is 10 mg taken once nightly, which should be taken 30 minutes prior to the intended bedtime and at least 7 hours prior to planned awakening. Belsomra has a long half-
life of 12 hours and steady state is achieved following once daily dosing at three days. If well tolerated, but not achieving the desired effect, the dose can be increased to a maximum of 20 mg. Providers are cautioned to use the lowest effective dose. Due to the potential for adverse events with increased dosage and long half-life of the drug, there should be continuous utilization of a least one week before increasing dosage.

**PROCEDURES AND BILLING CODES**

*To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.

- Code(s), if applicable.

**REFERENCES**

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- FDA Drug Safety Communication: Risk of next-morning impairment after use of insomnia drugs; FDA requires lower recommended doses for certain drugs containing zolpidem (Ambien, Ambien CR, Edular and Zolpimist), [http://www.fda.gov/drugs/drugsafety/UMC334033.THM 1-1013](http://www.fda.gov/drugs/drugsafety/UMC334033.THM 1-1013), Accessed March 28, 1014
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**POLICY HISTORY**

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