Sedative and Hypnotic Drug Therapy Policy

NOTICE

This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

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 (MT_1 and MT_2 agonists); and Silenor (doxepin) a tricyclic with a proposed mechanism of action as a H_1 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.

FDA-Approved Indications

- **Belsomra:** For the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.
- **Dayvigo:** 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) in adults and for the treatment of nighttime sleep disturbances in Smith-Magenis Syndrome (SMS) in patients 3 years of age and older.
- **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.

POLICY

Required Documentation:

Submission of the following information is necessary to initiate the prior authorization review on Hetlioz:

A. Initiation of therapy:
   1. Deletion at chromosome 17p11.2 (cytogenetic analysis or microarray) or a RAI1 gene mutation confirmed by genetic testing
B. Continuation of therapy:
   1. Medical records documenting a clinical response to threapy

Criteria for Initial Approval

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
   - The medication must be prescribed by or in consultation with 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 **6 months**

II. **Hetlioz** may be considered **medically necessary** for the treatment of sleep disturbances in Smith-Magenis syndrome when all of the following criteria are met:
   - Patient is ≥ 3 years of age
   - The patient has a diagnosis of Smith-Magenis syndrome confirmed by genetic testing showing a deletion at chromosome 17p11.2 (cytogenetic analysis or microarray) or a RAI1 gene mutation.
   - The medication must be prescribed by or in consultation with a sleep specialist or a specialist with expertise in the treatment of SMS
   - For requests for Hetlioz oral suspension, the patient must be unable to swallow Hetlioz capsules due to one of the following:
     - Age
     - Dysphagia
     - Oral/Motor difficulties
     - Medications are administered through a feeding tube

   Approval will be for **6 months**

III. **Belsomra and Dayvigo** 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 for Belsomra and 5 mg once nightly for Dayvigo.

Approval will be for **12 months**

IV. **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**

V. **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**

VI. **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**

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

Continuation of Therapy

I. The continuation of Belsomra, Dayvigo, Edluar, Intermezzo, Rozerem, Zolpimist, and Silenor may be considered **medically necessary** when the Criteria for Initial Approval above is met and the patient has a documented positive clinical response to Hetlioz therapy.

II. **Hetlioz** may be considered **medically necessary** for the continued treatment of Non-24-Hour Sleep-Wake Disorder (Non-24) when all of the following criteria are met:

- Patient has a documented positive clinical response to Hetlioz therapy (i.e., improvement in nighttime sleep, a decrease in daytime sleep, and improvement in functional impairment)
- The prescriber is a sleep specialist or has consulted with a sleep specialist
- Patient is totally blind with no visual light perception
- There is a documented diagnosis of Non 24 sleep-wake disorder by a sleep specialist

Approval will be for **12 months**

III. **Hetlioz** may be considered **medically necessary** for the continued treatment of nighttime sleep disturbances in Smith-Magenis syndrome when all of the following criteria are met:

- Patient has a documented positive clinical response to Hetlioz therapy (i.e., improvement in nighttime sleep quality and time and an improvement in functional impairment)
- The patient has a diagnosis of Smith-Magenis syndrome confirmed by genetic testing showing a deletion at chromosome 17p11.2 (cytogenetic analysis or microarray) or a RAI1 gene mutation.
- The medication must be prescribed by or in consultation with a sleep specialist or a specialist with expertise in the treatment of SMS
- For requests for Hetlioz oral suspension, the patient must be unable to swallow Hetlioz capsules due to one of the following:
  - Age
  - Dysphagia
  - Oral/Motor difficulties
  - Medications are administered through a feeding tube

Approval will be for **12 months**

Quantity Limits

- Belsomra 30 tablets/30 days
- Hetlioz 30 capsules/30 days

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 awaking 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.

Hetlioz is also approved for the treatment of nighttime sleep disturbances in Smith-Magenis syndrome (SMS) patients ≥16 years of age (capsules) or 3 to 15 years of age (oral suspension). SMS is a developmental disorder affecting about 1 in 15,000 to 25,000 births in the U.S. Patients with SMS present with a number of physical, mental and behavioral problems. The most common symptom of SMS is a severe sleep disorder associated with significant disruption in the lives of patients and their families. The effectiveness of Hetlioz in the treatment of nighttime sleep disturbances in SMS was established in a 9-

week, double-blind, placebo-controlled crossover study in 25 adults and pediatric patients with SMS. The primary endpoints were nighttime total sleep time and nighttime sleep quality from a parent/guardian-recorded diary. Nighttime total sleep time was reported as a time unit in hours and minutes. Nighttime sleep quality was rated as follows: 5 = excellent; 4 = good; 3 = average; 2 = fair; 1 = poor. The efficacy comparisons for nighttime sleep quality and total sleep time were based on the 50% of nights with the worst sleep quality and the 50% of nights with the least nighttime sleep in each 4-week period. Results showed that treatment with Hetlioz was associated with a statistically significant improvement in the 50% worst nights' sleep quality compared with placebo. While Hetlioz demonstrated improvements in the 50% worst total nighttime sleep time, the difference was not found to be statistically significant. The safety profile of Hetlioz was similar to that seen in previous studies for non-24-hour sleep-wake disorder.

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.

Dayvigo (lemborexant) is an additional orexin receptor antagonist, like Belsomra that was shown to improve sleep onset and sleep maintenance in clinical trials. In a phase 3, randomized controlled trial, both Dayvigo (lemborexant) 5 mg and 10 mg were superior to placebo and Ambien CR (zolpidem extended-release) 6.25 mg for the primary endpoint of latency to persistent sleep in patients age 55 years and older. In another phase 3, randomized controlled trial, both Dayvigo (lemborexant) 5 mg and 10 mg were superior to placebo for the primary endpoint of subjective sleep onset in patients age 18 years and older. In regards to safety, dose dependent somnolence was the most prominent adverse event occurring in ≥ 5% or more of patients. Cases of complex sleep behaviors, sleep paralysis, cataplexy-like symptoms, respiratory function in patients with respiratory disorders and worsening of depression/suicidal ideation were observed. Dayvigo is classified as a controlled substance (DEA schedule pending).

The recommended dose for Dayvigo (lemborexant) is 5 mg taken no more than once per night, immediately before going to bed, with at least 7 hours remaining before the planned time of awakening. The dose may be increased to the maximum recommended dose of 10 mg based on clinical response and tolerability. Time to sleep onset may be delayed if taken with or soon after a meal. Dayvigo (lemborexant) is available as 5 mg and 10 mg tablets.

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

- Ambien [Product information] Bridgewater, NJ: Sanofi-Aventis US, LLC, August 2019
- Ambien CR [Product information] Bridgewater, NJ: Sanofi-Aventis US, LLC, August 2019
- Sonata [Product information] Bristol, TN: King Pharmaceuticals, April, 2013
- Rozerem [Product information] Deerfield, IL: Takeda Pharmaceuticals America, Inc., December 2018.
- Lunesta [Product information] Marlborough, MA:, Sunovion Pharmaceuticals Inc., August 2019
- Zolpimist [Product information] Flemington, NJ: NovaDel Pharma Inc., August 2019.
- Carson S, Yen P-Y, McDonagh MS. Drug Class Review on Newer Drugs for Insomnia. 2006. http://www.ohsu.edu/drugeffectiveness/reports/final.cfm.
- Edluar [Product information] Somerset, NJ: August 2019
- Intermezzo [Product information] , Stamford, CT; Purdue Pharam L.P., September 2019
- FDA Drug Safety Communication: Risk of next-morning impariment after use of insomnia drugs; FDA requires lower recommneded doses for certain drugs containing zolpidem (Ambien, Ambien CR, Edular and Zolpimist), http://www.fda.gov/drugs/drugsafety/UMC334033.THM 1-1013, Accessed March 28,1014
- Hetlioz™ (tasimelteon) [prescribing information]. Vanda Pharmaceuticals, Inc. Washington, DC. December 2020.
- Morgenthaler TI, Lee-Chiong T, Alessi C, et al. Practice parameters for the clinical evaluation and treatment of circadian rhythm sleep disorders: an American Academy of Sleep Medicine report. Sleep. 2007;30(11):1445-1459.
- Sack RL, Lewy AJ. Circadian rhythm sleep disorders: lessons from the blind. *Sleep Med Rev*. 2001;5(3):189-206.
- Hack LM, Lockley SW, Arendt J, Skene DJ. The effects of low-dose 0.5-mg melatonin on the free-running circadian rhythms of blind subjects. *J Biol Rhythms*. 2003;18(5):420-429.
- Rozerem (ramelteon) [*prescribing information*]. Takeda Pharmaceuticals America, Inc. Deerfield, IL. November 2010.
- Vanda Pharmaceuticals. Tasimelteon. Advisory Committee Briefing Materials, November 14, 2013. Available at: http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/peripheralandcentralnervoussystemdrugsadvisorycommitee/ucm374388.pdf. Accessed April 2014.
- Herring WJ, Snyder E, Budd K, et al. Orexin receptor antagonism for treatment of insomnia. Neurology 2012;79:2265-2274.
- Belsomra® [prescribing information]. Merck & Co., Inc. Whitehouse Station, NJ. August 2014.
- Farkas, R. Suvorexant Safety and Efficacy. [powerpoint]. FDA. 2013. Available at: http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/peripheralandcentralnervoussystemdrugsadvisorycommittee/ucm354215.pdf. Accessed October 18, 2014.

- Morin AK, Jarvis CI, Lynch AM. Therapeutic options for sleep-maintenance and sleep-onset insomnia. Pharmacotherapy. 2007;27:89-110.
- Passarella S, Duong MT. Diagnosis and treatment of insomnia. Am J Health Syst Pharm. 2008;65:927-934.
- Drug Facts and Comparisons. Facts & Comparisons [database online]. St. Louis, MO: Wolters Kluwer Health, Inc; March 2005. Accessed October 20, 2014.
- Food and Drug Administration (FDA) Advisory Committee Meeting. Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee Meeting. [transcript]. May 22, 2013. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM362214.pdf. Accessed October 22, 2014.
- Food and Drug Administration (FDA). Center for Drug Evaluation and Research. Medical Review(s). Belsomra (suvorexant). FDA approval package for NDA 204569.
- Schutte-Rodin S, Broch L, Buysse D, et al. Clinical guideline for the evaluation and management of chronic insomnia in adults. American Academy of Sleep Medicine (AASM). J Clin Sleep Med 2008;4:487-504.
- Sateia MJ, Doghramji K, Hauri PJ, Morin CM. Evaluation of chronic insomnia. An American Academy of Sleep Medicine review. Sleep 2000;23(2):243-308.
- National Institutes of Health (NIH). National Institute of Health Science Conference statement on Manifestations and Management of Chronic Insomnia in Adults. June 13-15, 2005. Sleep 2005;28(9):1049-1057.
- Huedo-Medina TB, Kirsch I, Middlemass J, Klonizakis M, Siriwardena AN. Effectiveness of non-benzodiazepine hypnotics in treatment of adult insomnia: meta-analysis of data submitted to the Food and Drug Administration. BMJ 2012;345:e8343
- U.S. Food and Drug Administration Division of Neurology Products Center for Evaluation and Research. FDA Slide Presentation. Tasimelteon. FDA Presentations for the November 14, 2013 Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee. Available at: http://www.fda.gov/downloads/AdviosryCommittees/CommitteesMeetingMaterials/Drugs/peripheralandcentralnervoussystemdrugsadvisory committee/UCM376700.pdf. Accessed April 2014.
- Silenor [doxepin]. Somaxon Pharmaceuticals. Inc. San Diego, Ca. March 17, 2010.
- Intermezzo [zolpidem sublingual]. Facts & Comparisons ® eAnswers.
- http://online.factsandcomparisons.com. Accessed June 25, 2018.
- Dayvigo [prescribing information]. Eisai. Woodcliff Lake, NJ. December 2019.

*Some content reprinted from CVSHeatlh

POLICY HISTORY

Policy #: 05.01.64
Policy Creation: August 2007
Reviewed: January 2021
Revised: April 2020
Current Effective Date: March 8, 2021