



Medication Policy Manual

Policy No: dru350

Topic: Orally Administered Hypnotic Agents

Date of Origin: May 9, 2014

- zolpidem SL (generic, Edluar[®], Intermezzo[®])
- zolpidem oral spray (Zolpimist[®])
- ramelteon (Rozerem[®])
- suvorexant (Belsomra[®])

Committee Approval Date: July 14, 2017

Next Review Date: December 2017

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IMPORTANT REMINDER

This Medical Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medical policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Zolpidem sublingual “SL” (generic, Edluar, Intermezzo), Zolpidem oral spray (Zolpimist), ramelteon (Rozerem), and suvorexant (Belsomra) are orally administered hypnotic agents (sleep medicines) that are used for the treatment of insomnia. Zolpidem SL (generic, Edluar, Intermezzo), zolpidem oral spray (Zolpimist), and suvorexant (Belsomra) are controlled substances. Ramelteon (Rozerem) is not a controlled-substance.

Policy/Criteria

- I. Most contracts require prior authorization approval of zolpidem SL (generic, Edluar, Intermezzo), zolpidem oral spray (Zolpimist), ramelteon (Rozerem), and suvorexant (Belsomra) prior to coverage. Zolpidem SL (Edluar, Intermezzo), ramelteon (Rozerem), or suvorexant (Belsomra) may be considered medically necessary in patients with insomnia when criteria A through F below are met.
 - A. Difficulty initiating or maintaining sleep or early-morning awakening with inability to return to sleep has occurred for at least 3 nights per week and is present for at least 3 months.

AND

 - B. There is documentation that the insomnia has caused specific functional impairment. Examples of functional impairment include, but are not limited to, work-related impairment, academic impairment, or social impairment.

AND

 - C. The sleep disturbance is not due to untreated, reversible conditions. Other reversible conditions may include, but are not limited to, another sleep disorder, mental health disorder, or physiological effects of another substance.

AND

 - D. Non-pharmacologic therapies have been inadequate in improving functional impairments. Examples of non-pharmacologic therapies include, but are not limited to, stimulus control therapy, sleep restriction therapy, relaxation therapy, or cognitive therapy.

AND

 - E. Treatment with generic zolpidem immediate-release and one other generic medication used for sleep has been inadequate or not tolerated. (*see Appendix 1*)

AND

 - F. [*For zolpidem oral spray (Zolpimist) only*] Oral medications are not tolerated.
- II. Administration, Quantity Limitations, and Authorization Period
 - A. OmedaRx considers zolpidem SL (generic, Edluar, Intermezzo), zolpidem oral spray (Zolpimist), ramelteon (Rozerem), and suvorexant (Belsomra) to be self-administered medications.
 - B. When prior authorization is approved, zolpidem SL (generic, Edluar, Intermezzo), ramelteon (Rozerem), or suvorexant (Belsomra) may be authorized in quantities up to 30 tablets per month. Zolpidem oral spray (Zolpimist) may be authorized in quantities up to one spray bottle per month.

- C. Authorization shall be reviewed as follows to confirm that current medical necessity criteria are met and that there is clinical documentation of significantly improved functional impairment(s) due to treatment with zolpidem SL (generic, Edluar, Intermezzo), zolpidem oral spray (Zolpimist), ramelteon (Rozerem), or suvorexant (Belsomra).
1. **Initial Authorization:** Authorization shall be reviewed at 6 months.
 2. **Continued Authorization:** Continued authorization or re-authorization (after the initial 6 month period) shall be reviewed at least annually.
- III. Concomitant, alternating, or repeated sequential use of zolpidem SL (generic, Edluar, Intermezzo), zolpidem oral spray (Zolpimist), ramelteon (Rozerem), or suvorexant (Belsomra) with either zolpidem (Ambien, Edluar, Intermezzo, ZolpiMist), zolpidem ER (Ambien CR), eszopiclone (Lunesta), ramelteon (Rozerem), zaleplon (Sonata), or suvorexant (Belsomra) is considered duplication of therapy and not medically necessary.
- IV. Zolpidem SL (generic, Edluar, Intermezzo), zolpidem oral spray (Zolpimist), ramelteon (Rozerem), and suvorexant (Belsomra) are considered investigational when used for all other conditions other than those outlined in policy criteria above.

Position Statement

- Generic sleep medications provide the best value for members.
- Sleep medications such as zolpidem SL (generic, Edluar, Intermezzo), zolpidem oral spray (Zolpimist), ramelteon (Rozerem), and suvorexant (Belsomra) provide a modest benefit to help people fall asleep faster and stay asleep a little longer. The impact of this modest incremental benefit of sleep on a person's overall health is uncertain.
- Patients with nighttime sleep disturbances do not necessarily experience functional impairment. ^[1] Data supporting improvement in daytime function resulting from treatment with orally administered hypnotic agents are limited.
- OmedaRx coverage policy criteria are based on the Diagnostic and Statistical Manual of Mental Disorders "DSM-5" criteria for insomnia disorder. ^[1] (*See Appendix 2*)
- Organizations such as the National Sleep Foundation, the American Academy of Sleep Medicine, and the National Heart, Lung, and Blood Institute recommend non-pharmacologic (non-drug) methods as options to improve sleep quality. ^[2-4]
- Failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness, which should be evaluated.
- According to the American Academy of Sleep Medicine, psychological and behavioral interventions are effective and recommended as an initial intervention for the treatment of chronic insomnia when appropriate.

- In addition, the American Academy of Sleep Medicine recognizes the importance of treating comorbid conditions that commonly occur with insomnia and the modification of inappropriate caffeine, alcohol, and additional medications. When pharmacological treatment is warranted, treatment plans are tailored to individual diagnoses and primarily focus on sleep onset and/or sleep maintenance.

Clinical Efficacy

ZOLPIDEM SL (EDLUAR, INTERMEZZO)

- Zolpidem is a non-benzodiazepine hypnotic approved for the short-term treatment of insomnia. Despite the fact that it is not a benzodiazepine, it still has similar properties and is classified as a controlled substance.
- The safety and efficacy of zolpidem SL (generic, Edluar, Intermezzo) is based on prior zolpidem (Ambien) clinical trials.
- Zolpidem has shown modest benefit in helping people sleep. However, it has not been shown in clinical studies to improve health outcomes among people with insomnia. [5,6]
- Comparative trials have not demonstrated a clear benefit for zolpidem over other traditional therapies, such as short-acting benzodiazepines (such as triazolam or temazepam) or buspirone. [7-10]
 - * Zolpidem may be used for up to 4 weeks to treat subjective rebound insomnia. However, it has no advantage over temazepam at an equivalent dose. [10]
 - * Intermittent treatment with zolpidem (10 mg/day, 3-5 tablets/week, every other week up to 12 weeks) may be used for the treatment of insomnia disorder. [11]
- The safety and efficacy of using zolpidem beyond 35 days of treatment has not been studied in well-designed trials.
- There are no published trials evaluating the efficacy of zolpidem for the treatment of insomnia related to cancer.

RAMELTEON (ROZEREM)

- There is no evidence that ramelteon (Rozerem) therapy leads to clinically meaningful improvements in the health of patients.
- Ramelteon (Rozerem) is an agonist of the melatonin receptors (M1 and M2). However, ramelteon (Rozerem) has not been compared to other medications such as short-acting benzodiazepines in patients suffering from insomnia in published randomized, controlled trials. Therefore, conclusions cannot be drawn regarding safety or effectiveness when compared to other medications, such as short-acting benzodiazepines (e.g., triazolam or temazepam).
- There are two published trials evaluating the efficacy and safety of ramelteon (Rozerem). One trial evaluated the effects of ramelteon (Rozerem) for only 2 consecutive nights of therapy. [20]

- The other trial evaluated the effectiveness of ramelteon (Rozerem) up to 7 days. Ramelteon (Rozerem) may have been administered up to 35 days, but effectiveness was not studied for that duration of time. [21]
 - * After 5 weeks of treatment with ramelteon (Rozerem) 8 mg daily, patients reported a 13 minute reduction in sleep latency, compared with placebo.
 - * After 5 weeks of treatment with either ramelteon (Rozerem) 4 mg or 8 mg daily, there were no statistically significant differences in total sleep time compared to placebo.
- The US Agency for Healthcare Research and Quality (AHRQ) published a technical review on the management of chronic insomnia in adult patients and concluded that there is some evidence that melatonin is effective in the management of chronic insomnia in subsets of patients, and there is no evidence that melatonin poses a risk of harm, but more research is needed. [6]

SUVOREXANT (BELSOMRA)

- Suvorexant (Belsomra) is a non-benzodiazepine hypnotic approved for the short-term treatment of insomnia. Despite the fact that it is not a benzodiazepine, it still has similar properties and is classified as a controlled substance.
- In two clinical trials, suvorexant (Belsomra) had a modest benefit on the improvement in sleep maintenance and sleep onset. However, it has not been shown in clinical studies to improve health outcomes among people with insomnia. [22]
- * Quantitative differences in sleep maintenance between suvorexant (Belsomra) and placebo were ≤ 29 minutes at month one and ≤ 32 minutes at month three as estimated by polysomnography and a subjective patient-estimated assessment.
- * Quantitative differences in sleep latency between suvorexant (Belsomra) and placebo were ≤ 13 minutes at month one and ≤ 14 minutes at month three as estimated by polysomnography and a subjective patient-estimated assessment.
- Suvorexant (Belsomra) has not been compared to any other active treatments in clinical trials. Suvorexant (Belsomra) has only been compared to placebo. [22,23]
- The additional value of suvorexant (Belsomra) for the treatment of insomnia is uncertain as there is no data to compare its safety and efficacy versus any active comparators and currently, there are multiple generic treatment options for insomnia.
- Suvorexant (Belsomra) has only been studied for the treatment of insomnia. The use for all other conditions is considered investigational.
- Suvorexant (Belsomra) has been shown to be safe and effective at doses up to 20 mg per day, the maximum recommended daily dose.
- The American Academy of Sleep Medicine recommends initiation of psychological and/or behavioral therapy and individualized pharmacological treatment plans if needed. Pharmacologic treatment plans are tailored to individual diagnoses and primarily focus on sleep onset and/or sleep maintenance. [24]

- In addition, the guidelines do not recommend branded agents; however, they recognize that the initiation of drug therapy should be individualized.

Safety and Dosing

- The FDA labeling of hypnotics includes the following safety information [23,25-28]:
 - * After taking Edluar, Intermezzo, Zolpimist, Belsomra, or Rozerem you may get up out of bed while not being fully awake and do an activity that you do not know you are doing. The next morning, you may not remember that you did anything during the night. Reported activities include:
 - * driving a car (“sleep-driving”)
 - * making and eating food
 - * talking on the phone
 - * having sex
 - * sleep-walking
- The FDA has issued a drug safety communication regarding the risk of concomitant use of opiates and CNS depressants; serious adverse events including death have been reported. Health care professionals are advised to limit prescription of this combination to patients for whom alternative treatments are inadequate. The lowest effective dose and shortest duration of therapy should be utilized.

ZOLPIDEM SL (GENERIC, EDULAR, INTERMEZZO), ZOLPIDEM ORAL SPRAY (ZOLPIMIST), AND ZOLPIDEM ER (AMBIEN CR) [26,27,29]

- Zolpidem SL (generic, Edluar, Intermezzo) and zolpidem ER are classified as Class IV controlled substances, similar to the benzodiazepine class, and carry labeling warnings regarding risk of abuse and dependency.
- Guidelines recommend using the lowest effective dose of zolpidem SL and zolpidem ER. The recommended initial doses are as follows:

Medication	Recommended Dosing Per Night	
	Men	Women
zolpidem SL (Edluar)	5 - 10 mg	5 mg
zolpidem SL (Intermezzo)	3.5 mg	1.75 mg
zolpidem oral spray (Zolpimist)	5 - 10 mg	5 mg
Zolpidem ER (Ambien CR)	6.25 - 12.5 mg	6.25g

- The recommended initial doses for women and men are different because zolpidem clearance is lower in women.

RAMELTEON (ROZEREM) [31]

- Ramelteon (Rozerem) has not been proven to be safer or more effective than over-the-counter melatonin preparations in clinical studies.
- The recommended dose of ramelteon (Rozerem) is 8 mg taken within 30 minutes of going to bed. The total ramelteon (Rozerem) dose should not exceed 8 mg per day.
- Ramelteon (Rozerem) is not a controlled substance.

SUVOREXANT (BELSOMRA) [23]

- Suvorexant (Belsomra) carries the following warnings and precautions: daytime somnolence, need to evaluate for co-morbid diagnoses if insomnia persists after 7 – 10 days of treatment, nighttime “sleep driving” and other complex behaviors while out of bed and not fully awake, depression, compromised respiratory function, sleep paralysis, hallucinations, and cataplexy-like symptoms.
- The labeling states that a variety of cognitive and behavioral changes (e.g. amnesia, anxiety, hallucinations and other neuropsychiatric symptoms) have been reported to occur in association with the use of hypnotics such as suvorexant (Belsomra).

Appendix 1: Best Value Generic Prescription Medications Used for Sleep [24]
<i>Benzodiazepines</i>
estazolam flurazepam lorazepam temazepam triazolam quazepam
<i>Non-Benzodiazepines</i>
doxepin eszopiclone (generic Lunesta) trazodone zaleplon (generic Sonata) zolpidem immediate-release (generic Ambien) zolpidem extended-release (generic Ambien CR)

Appendix 2: Diagnostic criteria for Insomnia Disorder ^[1]

- A.** A predominant complaint of dissatisfaction with sleep quantity or quality, associated with one (or more) of the following symptoms:
1. Difficulty initiating sleep. (In children, this may manifest as difficulty initiating sleep without caregiver intervention.)
 2. Difficulty maintaining sleep, characterized by frequent awakenings or problems returning to sleep after awakenings. (In children, this may manifest as difficulty returning to sleep without caregiver intervention.)
 3. Early-morning awakening with inability to return to sleep.
- B.** The sleep disturbance causes clinically significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning.
- C.** The sleep difficulty occurs at least 3 nights per week.
- D.** The sleep difficulty is present for at least 3 months.
- E.** The sleep difficulty occurs despite adequate opportunity for sleep.
- F.** The insomnia is not better explained by and does not occur exclusively during the course of another sleep-wake disorder (e.g., narcolepsy, a breathing-related sleep disorder, a circadian rhythm sleep-wake disorder, a parasomnia).
- G.** The insomnia is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication).
- H.** Coexisting mental disorders and medical conditions do not adequately explain the predominant complaint of insomnia.

Cross References

None

Codes	Number	Description
N/A		

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29. Ambien CR® [package insert]. Bridgewater, NJ: Sanofi-Aventis; April 2013.
30. Lunesta® [package insert]. Marlborough, MA: Sunovion Pharmaceuticals; November 2012.
31. Rozerem® [package insert]. Deerfield, IL: Takeda Pharmaceuticals; November 2010.

Revision Date	Revision Summary
07/14/2017	Removed eszopiclone (Lunesta) and zolpidem ER (Ambien CR) from policy (effective 08/01/2017)
04/14/2017	Clarified criteria language; intent of policy coverage criteria unchanged
04/08/2016	Added zolpidem oral spray (Zolpimist) to policy