

Brand Name: Belsomra

Generic Name: suvorexant

Manufacturer: Merck & Co., Inc.

Drug Class: Sleep Aid

Uses^{1,2,3}:

Labeled Uses: Insomnia

Unlabeled uses: N/A

Mechanism of Action^{1,2,3}: The proposed mechanism of action of suvorexant is dual antagonism of central orexin receptors. Suvorexant blocks the binding of neuropeptides orexin A and B to receptors orexin 1 (OX1R) and orexin 2 (OX2R), respectively. The orexin neuropeptide signaling system is a central promoter of wakefulness. Blocking the binding of these wake-promoting neuropeptides is thought to suppress wake drive, exhibiting suvorexant's pharmacologic effect.

Pharmacokinetics:

Absorption and Distribution^{1,2,3}:

Tmax	2 hours
Vd	49 L
T 1/2	12 hours
Clearance	N/A
Protein binding	>99%
Bioavailability	82%

Metabolism^{1,2,3}: Suvorexant is extensively metabolized by the liver via CYP3A with minor contributions by CYP2C19. The primary metabolite, hydroxyl-suvorexant, is not thought to have any pharmacologic activity.

Elimination: Suvorexant is primarily excreted through the feces (66%) and to a lesser extent the urine (23%).

Efficacy:

Sun H, Kennedy WP, Wilbraham D, Lewis N, Calder N, Li X, Ma J, Yee KL, Ermlich S, Mangin E, Lines C, Rosen L, Chodakewitz J, Murphy GM. Effects of suvorexant, an orexin receptor antagonist, on sleep parameters as measured by polysomnography in healthy men. *Sleep*. 2013 Feb 1;36(2):259-67. doi: 10.5665/sleep.2386. PubMed PMID: 23372274; PubMed Central PMCID: PMC3542986.

Study Design: Randomized, double-blind, placebo-controlled, 4-period crossover PSG study, followed by an additional 5th period to assess pharmacokinetics.

Description of Study: *Methods*: 22 patients (all men) were enrolled. In periods 1-4 patients received the following treatments in a randomized order according to a balanced crossover design: suvorexant 10mg, 50mg, 100mg, and placebo. Subjects stayed overnight in a sleep laboratory for two 8-hour PSG recording sessions for each treatment period. Visual scoring of PSG data was performed by blinded personnel. Measures of sleep onset, sleep maintenance, sleep efficiency, and total sleep time were assessed. Psychomotor performance was assessed pre-dose and 10 hours post-dose using simple reaction time (SRT), choice reaction time (CRT), and digit symbol substitution tests (DSST). In treatment Period 5, subject randomly received suvorexant 10 mg, 50 mg, or 100 mg and stayed overnight for pharmacokinetic blood sampling throughout the night. *Results*: 19 men completed the study. Power spectral analysis showed that there was no statistically significant effect of suvorexant on Slow wave activity (SWA) during the first half of the night (placebo= 90.83; 100mg suvorexant= 89.67). For PSG sleep measures, suvorexant 50 mg and 100 mg statistically significantly decreased latency to persistent sleep (LPS) and time awake after sleep onset (WASO). A corresponding statistically significant increase in sleep efficiency (SE) and total sleep time (TST) was observed. There were no consistent statistically significant effects of suvorexant on PSG sleep architecture stages over the entire 8-h PSG recording session. At 100 mg, there was a statistically significant increase in reaction time for both SRT and CRT, but no statistically significant effect on the DSST. There were no statistically significant changes on SRT, CRT, and DSST at 10 and 50 mg. The median T_{max} was observed at 3 hours and the mean apparent terminal half-life was 9 to 13 hours. The most frequently reported adverse effect was somnolence and headache reported the morning after evening administration, and was more frequently reported by subjects receiving 100 mg (20%) than by subjects receiving 50 mg, 10 mg, or placebo (< 5%).

Limitations: The sample size was small (22 subjects enrolled and 19 completed). The sample size limits any efficacy data as well as pharmacokinetic data. All subjects were men, so extrapolation to the female sex is impossible with this study. Also, tests were performed in a sleep laboratory setting, much different than an at-home environment. The study was funded by Merck and all authors are either current or former employers of Merck.

Conclusion: This study showed that Suvorexant 50 mg and 100 mg decreased LPS and WASO and increased SE and TST in healthy male subjects without sleep disorders, while suvorexant 10 mg decreased WASO. This data shows that suvorexant may possess sleep-promoting effects both on sleep onset and sleep maintenance. Also, it appears that doses of 100 mg are associated with a greater increase in the amount of adverse effects of the drug, the most common being somnolence and

headache. At 10 mg and 50 mg, suvorexant did not show a statistically significant effect on any of the objective adverse effect evaluations.

Michelson D, Snyder E, Paradis E, Chengan-Liu M, Snavely DB, Hutzelmann J, Walsh JK, Krystal AD, Benca RM, Cohn M, Lines C, Roth T, Herring WJ. Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3 randomised, double-blind, placebo-controlled trial. *Lancet Neurol.* 2014 May; 13(5):461-71. doi: 10.1016/S1474-4422(14)70053-5. Epub 2014 Mar 27. PubMed PMID: 24680372.

Study Design: randomized, placebo-controlled, parallel-group trial at 106 investigational centers in the Americas, Australia, Europe, and South Africa from December, 2009, to August, 2011.

Description of Study: Methods: 781 patients enrolled. Patients were required to meet the DSM-IV criteria for primary insomnia. Patients were randomly assigned in a 2:1 ratio to receive either suvorexant or placebo for 12 months. At the conclusion of 12 months, randomly, half of the treatment group would continue receiving suvorexant, while the other half switched to placebo for 2 months. Thus, at the conclusion of the 14 month trial there would be 3 different groups of patients to study, suvorexant-suvorexant, suvorexant-placebo, and placebo-placebo. Patients received 40mg suvorexant nightly if they were younger than 65 years of age and 30mg if they were 65 years of age or older. Efficacy was assessed with an electronic morning sleep diary completed daily throughout the study by the patient that included several subjective measures (e.g. total sleep time, time to sleep onset). Outcomes: The primary objective for the 1-year phase was to assess the safety and tolerability of suvorexant. Secondary objectives were assessments of subjective total sleep time (sTST) and subjective time to sleep onset (sTSO) during the first month of treatment. Efficacy at later time points (months 2–12) were prespecified exploratory endpoints. Results: Safety and tolerability assessments through 1 year of treatment were the primary outcomes. No significant difference was found in the number of adverse events. Drug-related adverse events (as established by the investigator) were more prevalent in the treatment group (34.9%) as compared to the placebo group (20.5%). The most common adverse event was somnolence (13.2 % in treatment vs. 2.7% in placebo). Other statistically significant adverse events found to be more common in the treatment group include fatigue, dry mouth, dyspepsia, and peripheral edema. Subjective efficacy measures showing statistical significance as compared to placebo included total sleep time, time to sleep onset, and time awake after sleep onset at 1 month and 12 month measurements. There were no statistically significant differences with regard to worsening of sTST or sTSO for each night or for any of the three nights for the prespecified comparison of the suvorexant-placebo to the placebo-placebo group. However, the proportions of patients with rebound insomnia on all comparisons were numerically greater in the suvorexant-placebo group compared with the placebo-placebo group.

Limitations: Safety data is restricted to 1 year of use. No objective tests for efficacy. No objective tests for next-day effects (e.g. driving, reaction times). May not be able to extrapolate the data to patients with insomnia secondary to a condition. Dose response was not studied. Doses used were higher than the doses recently approved by the FDA.

Conclusions: Suvorexant was well tolerated through the trial, with no major adverse effects. The small number of sleep-hallucinations, sleep paralysis, and complex sleep-related behaviors were consistent with other insomnia drugs, and may be a class effect. There was no evidence for an effect on mood symptoms or suicidal ideation. The return of symptoms was worse by all measures in 1-year responders who discontinued treatment compared with responders who continued treatment, most patients retained some degree of treatment gain for the 2 months after suvorexant was discontinued.

Herring WJ, Snyder E, Budd K, Hutzelmann J, Snavely D, Liu K, Lines C, Roth T, Michelson D. Orexin receptor antagonism for treatment of insomnia: a randomized clinical trial of suvorexant. *Neurology*. 2012 Dec 4;79(23):2265-74. doi: 10.1212/WNL.0b013e31827688ee. Epub 2012 Nov 28. PubMed PMID: 23197752.

Study Design: randomized, double-blind, placebo-controlled, 2-period (4 weeks per period) crossover.

Description of Study: *Methods:* 254 patients were enrolled in the study. Patients received suvorexant (10 mg [n= 62], 20 mg [n =61], 40 mg [n= 59], or 80 mg [n =61]) in one period and placebo (n= 249) in the other. Polysomnography was performed on night 1 and at the end of week 4 of each period. The primary efficacy assessment was based on PSG measurement of sleep, with time in bed fixed at 8 hours from lights off to lights on with the lights-off time defined as +/- 10 minutes of the patient's reported median habitual bedtime. *Outcomes:* The co- efficacy end points were sleep efficiency (SE) on night 1 and at the end of week 4 and latency to persistent sleep (LPS) measured on night 1 and at the end of week 4. *Results:* A total of 228 patients completed the study. All doses of suvorexant were more effective than placebo in improving the co-primary end points of SE at night 1 and end of week 4. There was a dose-dependent relationship in findings at the end of week 1, as 10mg suvorexant improved SE by 5.2%, 20mg by 7.6%, 40mg by 10.8%, and 80mg by 12.9%. This trend was not seen at the end of 4 weeks, but all 4 doses did show statistical significance as compared to placebo. Also, exploratory endpoints of sTSO, sTST, and subjective quality of sleep measures at night 1 and end of week 4 showed that 40mg and 80mg doses of suvorexant were superior to placebo. A dose-related increase in adverse events was observed with suvorexant (any adverse events and those considered drug-related by the investigator); the 10mg and 20mg doses had a similar adverse event rate to placebo whereas the higher 40mg and 80mg doses showed an increase. The most common patient-reported adverse events with 4 or more occurrences on suvorexant were somnolence (drowsiness), headache, dizziness, abnormal dreams, upper respiratory tract infection, urinary tract infection, and increased alanine aminotransferase. There were no reports of cataplexy-like or somnambulism-like events. There were 2 reports of sleep paralysis, 2 reports of visual hallucinations and 1 report of excessive daytime sleepiness that lasted for approximately 4 hours.

Limitations: The total number of patients was relatively small. The treatment time (4 weeks) was short. Also, elderly patients were not evaluated. Pharmacokinetics were not evaluated. Next-day evaluations of driving and performance at work were not addressed though.

Conclusions: Suvorexant was superior to placebo in PSG as well as patient reported sleep measures both after 1 week and 4 weeks of treatment. The effects of suvorexant seem to be dose-dependent. 40mg and 80mg doses are associated with more adverse events, but are the most consistently effective doses as pertaining to the endpoints assessed. Overall suvorexant was well tolerated with most

common adverse effect being somnolence. Anterograde amnesia, a side effect that has been associated with benzodiazepine receptor agonist use, was not reported, nor were there adverse events indicative of potential for an abuse liability.

Contraindications:

Narcolepsy: The mechanism of action (orexin antagonism) may account for its ability to reduce signs of narcolepsy/cataplexy.

Precautions:

CNS Depression Effects and Daytime Impairment^{1,2,3}: suvorexant is a CNS depressant that can impair daytime wakefulness, even when used as prescribed. Co-administration with other CNS depressants increased the risk of CNS depression. Patients should be advised not to consume alcohol in combinations with suvorexant. Suvorexant can impair driving skills and may increase the risk of falling asleep while driving. Dose should be decreased in anyone who is experiencing daytime somnolence.

Need to Evaluate for Co-morbid Diagnoses¹: Sleep disturbances are often presentations of physical and/or psychiatric disorders. Treatment of insomnia should be initiated after a careful evaluation of the patients' current medical condition. Furthermore, treatment failure after 7-10 days may indicate the presence of a primary illness that needs to be evaluated. Worsening of insomnia or emergence of new cognitive or behavioral abnormalities may be due to an unrecognized psychiatric disorder and can emerge with treatment of hypnotic drugs.

Abnormal Thinking and Behavioral Changes^{1,3}: A variety of cognitive and behavioral changes have been reported in association with hypnotic drugs like suvorexant. These include but are not limited to amnesia, anxiety, and hallucinations upon sleep onset or awakening. Complex behaviors such as "sleep driving", preparing food, making phone calls, and having sex while being amnesic to the event have been reported in association with hypnotics. The use of alcohol and other CNS depressants may increase the risk of these behaviors.

Worsening of Depression/Suicidal Ideation^{1,3}: In clinical trials, a dose-dependent increase in suicidal ideation was observed in patients taking suvorexant. In primarily depressed patients treated with hypnotics, worsening of depression and suicidal thoughts and actions have been reported. The most common action in this group is intentional overdose. The lowest number of tablets that is feasible should be prescribed to a patient at any one time.

Compromised Respiratory Function^{1,3}: Sedative hypnotics have the potential to cause respiratory depression and/or oxygen desaturation, especially in patients with pre-existing pulmonary disease. Suvorexant has not been studied in patients with compromised respiratory function. The effects of suvorexant on respiratory function should be assessed when prescribing this medication to these patients. Benefits and risks should be weighed carefully

Sleep Paralysis, Hypnagogic/Hypnopompic Hallucinations, Cataplexy-like Symptoms^{1,3}:

Sleep paralysis, the inability to move or speak for several minutes upon sleep initiation or awakening can occur with suvorexant. Also, hypnagogic and hypnopompic hallucinations, including vivid and disturbing images can also occur while taking suvorexant.

Symptoms similar to cataplexy can occur while taking suvorexant. This may include periods of leg weakness lasting seconds to minutes that can occur at night as well as during the day, and may or may not be triggered by a physiologic event (e.g., laughter or surprise). The risk of these types of symptoms increases with increasing doses of suvorexant.

Adverse Effects^{1,2,3}:

Occurring in > 10 % of patients:

Endocrine:

Elevation of serum cholesterol (1 mg/dL with 10mg dose, 2 mg/dL with 20 mg dose, 3 mg/dL with 40 mg dose, and 6 mg/dL with 80 mg dose compared with a 4 mg/dL decrease observed with placebo)

Occurring in < 10 % and > 5% of patients:

Neurologic:

Somnolence (7%)

Headache (7%)

Occurring in < 5% of and > 1 % of patients:

Neurologic:

Dizziness (3%)

Gastrointestinal:

Diarrhea (2%)

Xerostomia (2%)

Respiratory:

Cough (2%)

Upper Respiratory Infection (2%)

Occurring in < 1% of patients, but clinically important:

Neurologic:

Cataplexy

Sleep paralysis

Psychiatric:

At risk for suicide

Disturbance in thinking (abnormal thinking)

Other:

Disturbance in sleep behavior (sleep-driving, sleep-eating, etc.)

Drug Interactions^{1,2,3}:

CNS-Active Agents:

When suvorexant was co-administered with alcohol, additive psychomotor impairment was demonstrated. However, no effect on pharmacokinetics was seen.

CYP3A Interactions:

Metabolism by liver enzyme CYP3A is the major elimination pathway of suvorexant. Other drugs and foods (e.g. grapefruit juice) that are metabolized by, inhibit, or induce CYP3A will have effects on suvorexant metabolism and subsequent serum levels. The manufacturer recommends against concomitant use of strong CYP3A inhibitors or inducers. A dose reduction is recommended when adding a moderate CYP3A inhibitor to a patient's regimen. When adding a mild to moderate CYP3A inducer, the patient should be monitored for decreased systemic exposure and lack of efficacy.

Digoxin:

Concomitant administration of suvorexant and digoxin leads to slightly increased digoxin levels due to inhibition of intestinal P-glycoprotein. Digoxin concentrations should be monitored when co-administering suvorexant with digoxin.

Dosing/Administration^{1,2,3}:

Adult Dosing: Initially 10mg once nightly taken within 30 minutes of bedtime, with at least 7 hours remaining before planned time of awakening.

Pediatric: Safety and Efficacy has not been established in pediatric patients.

Renal Impairment: No dosage adjustment is required in patients with renal impairment.

Hepatic Impairment:

Mild to moderate: No dosage adjustment necessary.

Severe: Use of suvorexant is not recommended.

Use in special circumstances^{1,2,3}:

Pregnancy:

Category C; There are no well controlled studies in pregnant women. Suvorexant should be used in pregnancy only if benefits outweigh the risks. Administration of suvorexant to pregnancy rats resulted in a decrease in fetal body weight at doses greater than 80mg/kg. Administration to pregnant rabbits resulted in no apparent adverse effects on embryo-fetal development. Excessive toxicity resulted in premature sacrifice of pregnant rabbits at 325 mg/kg. Administration of 30-200mg/kg of suvorexant to pregnant rats throughout gestation and lactation resulted in decreased body weight of the offspring at the highest dose tested. Plasma AUCs at the no-effect dose were approximately 25 times that in humans at the MRHD.

Lactation:

Suvorexant and its primary metabolite, hydroxyl-suvorexant, were excreted in rat milk at levels higher than that in the maternal plasma. It is not known whether this drug is excreted in human milk. Caution should be used when suvorexant is administered to a nursing mother.

Geriatrics:

Of the 1,784 patients treated in controlled clinical safety and efficacy trials, 829 patients were older than 65 years old and 159 patients were 75 years older. No clinically meaningful differences in safety and efficacy were observed between these patients and younger patients. However, in some studies, the dose given to patients older than 65 (30mg) was less than that given to younger patients (40mg). Other sedative hypnotics on the U.S. market are listed in the American Geriatrics Society's Beers Criteria as Potentially Inappropriate Medications to use in the elderly population. Caution should be used when administering suvorexant to patients in this population.

Conclusion:

Suvorexant is an effective agent for the indication of insomnia. Doses of 5,10,15 and 20mg are approved for use in the U.S. Suvorexant should be reserved for patients who can get at least 7 hours of sleep nightly. The half-life (9-13 hours) of suvorexant ties into its most common adverse effects of somnolence and headache seen the following morning and lasting into the day. These symptoms should be monitored and dosage adjusted accordingly. Worsening of mood and suicidal ideation have not been

shown to be statistically significant in clinical trials, but the recommendation of psychiatric evaluation prior to starting therapy still exists. Suvorexant is metabolized via CYP3A lending itself to potential drug interactions. Suvorexant may be superior to current therapy options when stopping therapy, as physical dependence and withdrawal symptoms in clinical trials seem to be minimal. This drug may also be a safer long-term option for patients who cannot quit medication treatment for insomnia. Its side effect profile will exclude some patients, but for those that can tolerate the drug and get the required amount of evening sleep, this drug may be superior to current options. Drug costs may limit its use initially, but with generic availability its use could become as widespread as current drugs indicated for insomnia.

Recommended References:

1. Product Information: BELSOMRA(R) oral tablets, suvorexant oral tablets. Merck Sharp & Dohme Corp. (per manufacturer), Whitehouse Station, NJ, 2014.
2. Suvorexant. In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically.
3. Suvorexant. Clinical Pharmacology [Internet database] Gold Standard, Inc., 2007. Available at <http://www.clinicalpharmacology.com>. Accessed August 25, 2014.
4. Sun H, Kennedy WP, Wilbraham D, Lewis N, Calder N, Li X, Ma J, Yee KL, Ermlich S, Mangin E, Lines C, Rosen L, Chodakewitz J, Murphy GM. Effects of suvorexant, an orexin receptor antagonist, on sleep parameters as measured by polysomnography in healthy men. *Sleep*. 2013 Feb 1;36(2):259-67. doi: 10.5665/sleep.2386. PubMed PMID: 23372274; PubMed Central PMCID: PMC3542986.
5. Michelson D, Snyder E, Paradis E, Chengan-Liu M, Snively DB, Hutzelmann J, Walsh JK, Krystal AD, Benca RM, Cohn M, Lines C, Roth T, Herring WJ. Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3 randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2014 May; 13(5):461-71. doi: 10.1016/S1474-4422(14)70053-5. Epub 2014 Mar 27. PubMed PMID: 24680372.
6. Herring WJ, Snyder E, Budd K, Hutzelmann J, Snively D, Liu K, Lines C, Roth T, Michelson D. Orexin receptor antagonism for treatment of insomnia: a randomized clinical trial of suvorexant. *Neurology*. 2012 Dec 4;79(23):2265-74. doi: 10.1212/WNL.0b013e31827688ee. Epub 2012 Nov 28. PubMed PMID: 23197752.

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