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Formulary Drug Reviews

Suvorexant

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Generic Name:	Suvorexant
Proprietary Name:	*Belsomra* (Merck)
Approval Rating:	1S
Therapeutic Class:	Orexin receptor antagonists; sedatives and hypnotics, nonbarbiturate
Similar Drugs:	None
Sound- and Look-Alike Names:	*Serevent*

INDICATIONS

Suvorexant is indicated for the treatment of insomnia, which is characterized by difficulties with sleep onset and/or sleep maintenance.[1] The US Food and Drug Administration (FDA)–approved indications for the nonbenzodiazepine hypnotics are compared in **Table 1**.[2-7]

CLINICAL PHARMACOLOGY

Suvorexant is a dual orexin receptor antagonist, binding the orexin-1 and orexin-2 receptors. Endogenous orexin A and B bind to the orexin receptors and are involved with the regulation of arousal and wakefulness. Suvorexant is able to block the effects of the orexin compounds and promote sleep.[8-10] In animal models, suvorexant dose-dependently reduced locomotor activity and promoted sleep.[9] In healthy human subjects, suvorexant was associated with a dose-dependent increase in sleepiness and decrease in alertness.[11]

Suvorexant appears to have a lack of effect on sleep neurophysiology. Minimal electroencephalographic changes were observed during rapid eye movement (REM) and non-REM sleep following the administration of suvorexant to patients with primary insomnia and to healthy volunteers.[12,13]

PHARMACOKINETICS

Following oral administration, the median time-to-peak concentration (T_{max}) is 2 hours (range, 30 minutes to 6 hours).[1,13] Mean absolute bioavailability of the 10 mg dose is 82%. Exposure increases in a slightly less than dose-proportional manner over the range of 10 to 80 mg because of reduced

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Table 1. US Food and Drug Administration–approved indications for nonbenzodiazepine hypnotics [1-7]

Agent	Class	Indications		
		Treatment of insomnia characterized by difficulty with sleep onset	Treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance	Treatment of insomnia characterized by difficulties with sleep maintenance
Suvorexant	Orexin receptor antagonist		X	
Doxepin	Tricyclic antidepressant			X
Eszopiclone	Benzodiazepine receptor agonist		X	
Ramelteon	Melatonin receptor agonist	X		
Zaleplon	Benzodiazepine receptor agonist	X		
Zolpidem extended release	Benzodiazepine receptor agonist		X	
Zolpidem immediate release	Benzodiazepine receptor agonist	X		

absorption at higher doses.[1] Ingestion with a high-fat meal resulted in delayed T_{max}.[1] Suvorexant is highly plasma-protein bound (greater than 99%).[1]

Suvorexant is primarily eliminated via cytochrome P450 (CYP-450) 3A metabolism, with less elimination via CYP2C19 metabolism. The primary metabolite, hydroxy-suvorexant, is not active.[1] The mean terminal elimination half-life is approximately 12 hours.[1,11,13] The primary route of elimination is through the feces.[1] Its volume of distribution is 49 L.[1]

Suvorexant exposure is higher in females than in males, with the area under the curve (AUC) increased 17% and the peak concentration (C_{max}) increased 9%.[1] Suvorexant clearance is inversely related to body mass index (BMI). In obese patients, the AUC is increased 31% and C_{max} is increased 17% compared with subjects with a normal BMI. In obese females, the AUC and C_{max} are increased 46% and 25% compared with nonobese females.[1] Suvorexant half-life was increased in subjects with moderate hepatic impairment (19 vs 15 hours); however, exposure did not differ.[1] Suvorexant exposure did not differ between subjects with severe renal impairment and healthy matched controls.[1] Age and race do not appear to have any clinically important effect on suvorexant pharmacokinetics.[1]

COMPARATIVE EFFICACY

Indication: Insomnia

Guidelines

Guideline: Clinical guideline for the evaluation and management of chronic insomnia in adults

Reference: Schutte-Rodin S, et al, 2008[14]

Comments: Selection of a pharmacotherapy should be guided by the symptom pattern, treatment goals, past treatment responses, patient preferences, cost, availability of other treatments, comorbid conditions, contraindications, concurrent medication interactions, and adverse effects. The recommended initial medication trials should be with short- to intermediate-acting benzodiazepine receptor agonists (benzodiazepines or benzodiazepine receptor agonists such as zolpidem, eszopiclone, zaleplon, and temazepam) or ramelteon. If the initial agent is not effective, then an alternate short- to intermediate-acting benzodiazepine receptor agonist or ramelteon should be tried. Sedating antidepressants, especially when used in the management of comorbid depression or anxiety, may be tried next; examples of these agents include trazodone, amitriptyline, doxepin, and mirtazapine. The next step can be combined use of a sedating antidepressant

with a benzodiazepine receptor agonist or ramelteon. Antiepilepsy medications (eg, gabapentin, tiagabine) and atypical antipsychotics (eg, quetiapine, olanzapine) should only be used in patients with comorbid insomnia who may benefit from the primary action of the drugs as well as from their sedating effects. Nonprescription antihistamine and antihistamine/analgesic agents and herbal and nutritional supplements are not recommended for the treatment of chronic insomnia due to the lack of efficacy and safety data. Older approved agents for insomnia, such as barbiturates and chloral hydrate, are also not recommended. The guideline advises that hypnotic therapy should be supplemented with behavioral and cognitive therapies when possible, along with patient education.

Studies

Drug: Suvorexant vs Placebo

Reference: Connor K, et al, 2012 (Study P028)[15,16]

Study Design: Randomized, double-blind, placebo-controlled, multicenter study

Study Funding: Merck

Patients: 1,022 patients with primary insomnia; 1,021 received at least 1 dose of the study medication. Mean age of patients was 56 years (range, 18 to 87 years), with 42% elderly (65 years and older); 62.4% were female; 65.1% of patients were White, 25.8% were Asian, and 5.7% were Black; and 35% were from Europe, 33.9% were from North America, and 24.2% were from Japan.

Intervention: Suvorexant 20 mg (15 mg for patients 65 years and older), 40 mg (30 mg for patients 65 years and older), or placebo for 3 months, with an optional 3-month double-blind extension and a 1-week double-blind run-out at the conclusion of treatment.

Results

Primary Endpoint(s):

- Change from baseline in subjective total sleep time (TST) at week 1 (high dose vs placebo): 21.4 minutes greater with suvorexant ($P < .001$).
- Change from baseline in subjective TST at month 1 (high dose vs placebo): 19.6 minutes greater with suvorexant ($P < .001$).
- Change from baseline in subjective TST at month 3 (high dose vs placebo): 19.7 minutes greater with suvorexant ($P < .001$).
- Change from baseline in wake time after sleep onset (WASO) at night 1 (high dose vs placebo): reduced 38.4 minutes with suvorexant relative to placebo ($P < .001$).
- Change from baseline in WASO at month 1 (high dose vs placebo): reduced 26.3 minutes with suvorexant relative to placebo ($P < .001$).
- Change from baseline in WASO at month 3 (high dose vs placebo): reduced 22.9 minutes with suvorexant relative to placebo ($P < .001$).
- Change from baseline in subjective time to sleep onset (TSO) at week 1 (high dose vs placebo): reduced 5.7 minutes with suvorexant relative to placebo ($P = .0061$).
- Change from baseline in subjective TSO at month 1 (high dose vs placebo): reduced 7.4 minutes with suvorexant relative to placebo ($P = .003$).
- Change from baseline in subjective TSO at month 3 (high dose vs placebo): reduced 8.4 minutes with suvorexant relative to placebo ($P < .001$).
- Change from baseline in latency to onset of persistent sleep on night 1 (high dose vs placebo): reduced 10.3 minutes with suvorexant relative to placebo ($P < .001$).
- Change from baseline in latency to onset of persistent sleep at month 1 (high dose vs placebo): reduced 11.2 minutes with suvorexant relative to placebo ($P < .001$).
- Change from baseline in latency to onset of persistent sleep at month 3 (high dose vs placebo): reduced 9.4 minutes with suvorexant relative to placebo ($P < .001$).

Secondary Endpoint(s):

- Change from baseline in subjective TST at week 1 (low dose vs placebo): 13.6 minutes greater with suvorexant ($P < .001$).
- Change from baseline in subjective TST at month 1 (low dose vs placebo): 16.3 minutes greater with suvorexant ($P < .001$).
- Change from baseline in subjective TST at month 3 (low dose vs placebo): 10.7 minutes greater with suvorexant ($P = .017$).
- Change from baseline in WASO at night 1 (low dose vs placebo): reduced 32.5 minutes with suvorexant relative to placebo ($P < .001$).
- Change from baseline in WASO at month 1 (low dose vs placebo): reduced 26.4 minutes with suvorexant relative to placebo ($P < .001$).

- Change from baseline in WASO at month 3 (low dose vs placebo): reduced 16.6 minutes relative to placebo ($P < .001$).
- Change from baseline in subjective TSO at week 1 (low dose vs placebo): reduced 5.6 minutes with suvorexant relative to placebo ($P = .016$).
- Change from baseline in subjective TSO at month 1 (low dose vs placebo): reduced 5.4 minutes with suvorexant relative to placebo ($P = .052$).
- Change from baseline in subjective TSO at month 3 (low dose vs placebo): reduced 5.2 minutes with suvorexant relative to placebo ($P = .04$).
- Change from baseline in latency to onset of persistent sleep on night 1 (low dose vs placebo): reduced 9.6 minutes with suvorexant relative to placebo ($P < .001$).
- Change from baseline in latency to onset of persistent sleep at month 1 (low dose vs placebo): reduced 10.3 minutes with suvorexant relative to placebo ($P < .001$).
- Change from baseline in latency to onset of persistent sleep at month 3 (low dose vs placebo): reduced 8.1 minutes with suvorexant relative to placebo ($P = .0061$).

Comments: Adherence with the prescribed study medication was 98% in all treatment groups. Differences between the 20 or 15 mg dose and placebo were smaller than differences between the 40 or 30 mg dose and placebo, although most remained significant. No clinically important rebound or withdrawal was observed by the investigators following discontinuation of suvorexant therapy. Discontinuations due to adverse effects occurred in 3.9% of patients receiving high-dose suvorexant, 2.4% of those receiving low-dose suvorexant, and 5.5% of those receiving placebo.

Limitations: Presented only as a meeting abstract and in the FDA briefing document.

Reference: Ivgy-May N, et al, 2012 (Study P029)[16-18]

Study Design: Randomized, double-blind, placebo-controlled, multicenter study

Study Funding: Merck

Patients: 1,019 patients with primary insomnia; 1,009 received at least 1 dose of the study medication. Mean age of patients was 56 years (range, 18 to 86 years), with 41% elderly (65 years or older); 66.5% were female; 80.2% of patients were White, 7.7% were Asian, and 4.5% were Black; and 30.2% were from Europe and 48% were from North America.

Intervention: Suvorexant 20 mg (15 mg for patients 65 years and older), 40 mg (30 mg for patients 65 years and older), or placebo for 3 months, with an optional 3-month double-blind extension and a 1-week double-blind run-out at the conclusion of treatment.

Results

Primary Endpoint(s):

- Change from baseline in subjective TST at week 1 (high dose vs placebo): 26.4 minutes greater with suvorexant than placebo ($P < .001$).
- Change from baseline in subjective TST at month 1 (high dose vs placebo): 26.3 minutes greater with suvorexant than placebo ($P < .001$).
- Change from baseline in subjective TST at month 3 (high dose vs placebo): 25.1 minutes greater with suvorexant than placebo ($P < .001$).
- Change from baseline in WASO at night 1 (high dose vs placebo): reduced 42 minutes with suvorexant relative to placebo ($P < .001$).
- Change from baseline in WASO at month 1 (high dose vs placebo): reduced 29.4 minutes with suvorexant relative to placebo ($P < .001$).
- Change from baseline in WASO at month 3 (high dose vs placebo): reduced 29.4 minutes with suvorexant relative to placebo ($P < .001$).
- Change from baseline in subjective TSO at week 1 (high dose vs placebo): reduced 13.1 minutes with suvorexant relative to placebo ($P < .001$).
- Change from baseline in subjective TSO at month 1 (high dose vs placebo): reduced 12.8 minutes with suvorexant relative to placebo ($P < .001$).
- Change from baseline in subjective TSO at month 3 (high dose vs placebo): reduced 13.2 minutes with suvorexant relative to placebo ($P < .001$).
- Change from baseline in latency to onset of persistent sleep on night 1 (high dose vs placebo): reduced 21.7 minutes with suvorexant relative to placebo ($P < .001$).
- Change from baseline in latency to onset of persistent sleep at month 1 (high dose vs placebo): reduced 12.1 minutes with suvorexant relative to placebo ($P < .001$).
- Change from baseline in latency to onset of persistent sleep at month 3 (high dose vs placebo): reduced 3.6 minutes with suvorexant relative to placebo ($P = .27$).

Secondary Endpoint(s):

- Change from baseline in subjective TST at week 1 (low dose vs placebo): 16.8 minutes greater with suvorexant than placebo ($P < .001$).
- Change from baseline in subjective TST at month 1 (low dose vs placebo): 20.9 minutes greater with suvorexant than placebo ($P < .001$).
- Change from baseline in subjective TST at month 3 (low dose vs placebo): 22.1 minutes greater with suvorexant than placebo ($P < .001$).
- Change from baseline in WASO at night 1 (low dose vs placebo): reduced 37 minutes with suvorexant relative to placebo ($P < .001$).
- Change from baseline in WASO at month 1 (low dose vs placebo): reduced 24.1 minutes with suvorexant relative to placebo ($P < .001$).
- Change from baseline in WASO at month 3 (low dose vs placebo): reduced 31.1 minutes with suvorexant relative to placebo ($P < .001$).
- Change from baseline in subjective TSO at week 1 (low dose vs placebo): reduced 7.5 minutes with suvorexant relative to placebo ($P = .006$).
- Change from baseline in subjective TSO at month 1 (low dose vs placebo): reduced 6.9 minutes with suvorexant relative to placebo ($P = .05$).
- Change from baseline in subjective TSO at month 3 (low dose vs placebo): reduced 7.6 minutes with suvorexant relative to placebo ($P = .04$).
- Change from baseline in latency to onset of persistent sleep on night 1 (low dose vs placebo): reduced 12.4 minutes with suvorexant relative to placebo ($P = .004$).
- Change from baseline in latency to onset of persistent sleep at month 1 (low dose vs placebo): reduced 7.8 minutes with suvorexant relative to placebo ($P = .03$).
- Change from baseline in latency to onset of persistent sleep at month 3 (low dose vs placebo): reduced 0.3 minutes with suvorexant relative to placebo ($P = .93$).

Comments: Adherence with the prescribed study medication as 98% in all treatment groups. Differences between the 20 or 15 mg dose and placebo were smaller than differences between the 40 or 30 mg dose and placebo. No clinically important rebound or withdrawal was observed by the investigators following discontinuation of suvorexant therapy. Discontinuations due to adverse effects occurred in 4.8% of patients receiving high-dose suvorexant, 4.2% of patients receiving low-dose suvorexant, and 4.4% of patients receiving placebo.

The 2 pivotal efficacy studies were P028 and P029. Both studies were similar in design and provided 3-month treatment data for the primary efficacy assessment. Both P028 and P029 showed that the high-dose suvorexant was better than placebo in sleep maintenance and sleep onset throughout the study. The lower dose group was not the primary focus of the study but did show some efficacy on sleep maintenance and inconsistent improvements in sleep onset.[16]

Limitations: Presented only as a meeting abstract and in the FDA briefing document.

Reference: Michelson D, et al, 2014 (Study P009)[16,19-22]

Study Design: Randomized, double-blind, placebo-controlled, 12-month, multicenter study

Study Funding: Merck

Patients: 781 patients with primary insomnia; percent younger than 65 years (approximately 41%) and 65 years and older (59%) were similar in both groups.

Intervention: Patients were randomly assigned to suvorexant ($n = 522$) or placebo ($n = 259$) nightly for 12 months using a 2:1 ratio. The dose of suvorexant was 40 mg for patients 18 to 64 years of age and 30 mg for patients 65 years and older. After 12 months, patients treated with suvorexant were re-randomized to either suvorexant or placebo for 2 months, whereas those originally assigned the placebo remained on placebo for this 2-month period.

Results

Primary Endpoint(s):

- Safety and tolerability: Over 1 year, 69.5% of patients treated with suvorexant and 63.6% treated with placebo experienced an adverse event. Serious adverse events were reported in 5.2% of patients treated with suvorexant and 6.6% treated with placebo. Somnolence was the most common adverse event, reported in 13.2% of patients treated with suvorexant compared with 2.7% treated with placebo. Other adverse events that occurred more frequently with suvorexant than placebo were fatigue and dry mouth. Discontinuation due to adverse events occurred in 11.7% in the suvorexant group

compared with 8.5% in the placebo group. Suicidal ideation occurred in 4 patients treated with suvorexant and none treated with placebo. Other predefined events of clinical interest included somnambulism (1 event), hypnagogic hallucination (3 events), hypnopompic hallucination (1 event), and sleep paralysis (2 events), all of which occurred in suvorexant-treated patients. Excessive daytime sleepiness was reported in 2.5% of suvorexant-treated patients and 0.8% of placebo-treated patients. Motor vehicle accidents or citations were reported in 6% of suvorexant-treated patients and 4% of placebo recipients.

Secondary Endpoint(s):

- Mean change from baseline in self-reported TST after 1 month of treatment: 22.7 minutes greater with suvorexant than with placebo (95% CI, 16.4% to 29%; $P < .001$).
- Mean change from baseline in self-reported TSO after 1 month of treatment: 9.5 minutes sooner with suvorexant than with placebo (95% CI, –14.6 to –4.5; $P < .001$).

Other Endpoint(s):

- Mean change from baseline in self-reported WASO after 1 month of treatment: 9 minutes less with suvorexant than with placebo (95% CI, –13.8 to –4.1; $P < .001$).
- Mean change from baseline in self-reported TST, TSO, and WASO at each month over 12 months: suvorexant results were reported to be maintained over the 12-month evaluation period ($P < .05$).
- Suvorexant was better than placebo at month 1 and 12 for several diary measures (WASO, quality of sleep, and refreshed feeling on waking; all Ps < .05) but not for the measure of number of awakenings. Suvorexant was better than placebo at month 1 and 12 for all rating scale endpoints (Insomnia Severity Index, Clinician Global Impression of Severity, Patient Global Impression of Severity, Clinical Global Impression of Improvement, and Patient Global Impression of Improvement; all Ps < .05). No difference between treatments was observed in the measure of mood (Quick Inventory of Depressive Symptomatology).
- Rebound insomnia measures were not significantly worse among patients switched from suvorexant to placebo compared with those remaining on placebo; however, the proportion of patients with rebound insomnia was greater numerically in the group discontinued from suvorexant.
- Three or more withdrawal symptoms on the Tyrer Withdrawal Symptom Questionnaire on any of the first 3 nights after discontinuation were reported in no more than 3.2% of patients in any treatment group, with no difference between treatments.

Comments: Insomnia symptoms returned within 1 week of discontinuation of suvorexant therapy.

Limitations: Study doses were higher than the FDA-approved doses. The 1-year phase of the study was completed by 62% of the patients randomly assigned to receive suvorexant and 63% assigned to receive placebo.

Reference: Herring WJ, et al, 2012; *Belsomra* prescribing information, 2014 (Study P006)[1,16,23]

Study Design: Randomized, double-blind, double-dummy, placebo-controlled, multicenter, crossover study

Study Funding: Merck Research Laboratories

Patients: 249 patients 18 to 64 years of age (mean, 44 years) with primary insomnia, polysomnography assessed with latency to persistent sleep of at least 20 minutes, and a mean wake time after sleep onset of at least 60 minutes. At baseline, mean sleep efficiency was 66%, mean TST was 316 minutes, average WASO was 101 minutes, and mean latency to persistent sleep was 69 minutes. Of the patients, 59% were women and 70% were White; 87% were from the United States and 13% were from Japan.

Intervention: Suvorexant 10, 20, 40, or 80 mg nightly for 4 weeks and placebo nightly for 4 weeks.

Results

Primary Endpoint(s):

- Sleep efficiency (TST divided by time in bed in minutes) on night 1: increased with each suvorexant dose relative to placebo (5.2% with the 10 mg dose, $P \leq .01$; 7.6% with the 20 mg dose, $P \leq .001$; 10.8% with the 40 mg dose, $P \leq .001$; 12.9% with the 80 mg dose, $P \leq .001$).
- Sleep efficiency at the end of week 4: increased with each suvorexant dose relative to placebo (4.7% with the 10 mg dose, $P \leq .01$; 10.4% with the 20 mg dose, $P \leq .001$; 7.8% with the 40 mg dose, $P \leq .001$; and 7.6% with the 80 mg dose, $P \leq .001$).

Secondary Endpoint(s):

- WASO on night 1: reduced with each suvorexant dose relative to placebo (–21.2 minutes with the 10 mg dose, –24.7 minutes with the 20 mg dose, –33.9 minutes with the 40 mg dose, –36.8 minutes with the 40 mg dose; all Ps ≤ .001).

- WASO at the end of week 4: reduced with each suvorexant dose relative to placebo (–21.4 minutes with the 10 mg dose, –28.1 minutes with the 20 mg dose, –33.2 minutes with the 40 mg dose, –28.9 minutes with the 40 mg dose; all *P*s ≤ .001).
- Latency to persistent sleep on night 1: reduced with the suvorexant 40 and 80 mg doses relative to placebo (–23.1 minutes with the 40 mg dose, –25.4 minutes with the 80 mg dose; both *P*s ≤ .001).
- Latency to persistent sleep at the end of week 4: reduced only with the suvorexant 20 mg dose relative to placebo (–22.3 minutes, $P \leq .001$).

Other Endpoint(s):

- TST on night 1: increased with each suvorexant dose relative to placebo (25.1 minutes with the 10 mg dose, $P \leq .01$; 36.2 minutes with the 20 mg dose, $P \leq .001$; 52.4 minutes with the 40 mg dose, $P \leq .001$; 61.9 minutes with the 80 mg dose, $P \leq .001$).
- TST at the end of week 4: increased with each suvorexant dose relative to placebo (22.3 minutes with the 10 mg dose, $P \leq .01$; 49.9 minutes with the 20 mg dose, $P \leq .001$; 36.8 minutes with the 40 mg dose, $P \leq .001$; 36.6 minutes with the 80 mg dose, $P \leq .001$).
- Number of awakenings: reduced only with the 80 mg dose on night 1 (–3.3, $P \leq .001$).
- Residual effects were not consistently observed using the Digit Symbol Copy Test and Digit Symbol Substitution Test.

Limitations: The study had 95% power to detect a 40-minute difference in TST (an 8.3% change in sleep efficiency) and 93% power to detect a clinically relevant difference in WASO but only 64% power to detect a clinically relevant difference in latency to persistent sleep. Study duration was short. Elderly patients were excluded from the study population.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications

Suvorexant is contraindicated in patients with narcolepsy.[1] **Table 2** summarizes the contraindications, warnings, and precautions for the nonbenzodiazepine sedative hypnotics used in the treatment of insomnia.

Warnings and Precautions

Suvorexant is a central nervous system (CNS) depressant and may impair daytime wakefulness even when taken as recommended. It can impair driving skills and may increase the risk of falling asleep while driving. Impaired driving ability was seen in some patients taking a 20 mg dose. Patients taking the 20 mg dose should be advised against next-day driving and other activities requiring full mental alertness. Caution is also advised in patients taking lower doses. The risk of next-day impairment is increased if suvorexant is taken with less than a full night of sleep remaining, if a higher than recommended dose is taken, if it is coadministered with other CNS depressant medications or alcohol, or if it is coadministered with other drugs that increase blood levels of suvorexant.[1]

In studies of the residual effects of single and repeated evening doses of suvorexant 15 and 30 mg in 24 healthy elderly subjects and 20 and 40 mg in 28 nonelderly subjects on highway driving, suvorexant was not associated with clinically important mean changes in the standard deviation of lateral position, a measure of "weaving" in a highway driving test, conducted the next morning; however, impaired driving performance was observed in some subjects. In addition, 5 subjects (4 nonelderly subjects on suvorexant and 1 elderly subject on placebo) prematurely stopped their driving tests due to somnolence.[1,24] Next-day impairment of memory and balance were not observed in 3 studies but were observed in a fourth study in healthy nonelderly subjects exposed to suvorexant at bedtime.[1]

Underlying physical and/or psychiatric disorders should be considered prior to initiating therapy for a sleep disturbance. Failure of insomnia to remit after 7 to 10 days of therapy may indicate the presence of an underlying disorder that should be evaluated.[1]

Cognitive and behavioral changes, including amnesia, anxiety, hallucinations, and other neuropsychiatric symptoms, have been reported with the use of hypnotics such as suvorexant. Complex behaviors such as "sleep-driving" have also been reported. The use of alcohol and other CNS depressants may increase the risk of these behaviors. Discontinuation of therapy should be strongly considered in patients who report any complex sleep behavior.[1]

A dose-dependent increase in suicidal ideation was observed in patients taking suvorexant in clinical trials. Patients with suicidal ideation or any new behavioral sign or symptom should be immediately evaluated.[1]

Suvorexant has not been studied in patients with severe obstructive sleep apnea or severe chronic obstructive pulmonary disease (COPD). In patients with mild to moderate obstructive sleep apnea and mild to moderate COPD, significant respiratory

Table 2. Contraindications, warnings, and precautions for the nonbenzodiazepine sedative hypnotics used in the treatment of insomnia[1-7]

	Suvorexant	Doxepin	Eszopiclone	Ramelteon	Zaleplon	Zolpidem	Zolpidem extended-release
Contraindications							
Narcolepsy	X						
Hypersensitivity/angioedema/anaphylaxis		X	X	X	X	X	X
Concomitant fluvoxamine				X			
Concurrent monoamine oxidase inhibitor or use within 2 weeks		X					
Untreated narrow-angle glaucoma or severe urinary retention		X					
Warnings and precautions							
CNS depressant effects	X	X	X	X	X	X	X
Daytime or next-day impairment	X	X	X			X	X
Evaluation for comorbid diagnoses	X	X	X	X	X	X	X
Abnormal thinking and behavioral changes	X	X	X	X	X	X	X
Worsening of depression/suicidal ideation	X	X	X	X	X	X	X
Compromised respiratory function	X	X	X	X	X	X	X
Sleep paralysis, hypnagogic hallucinations, cataplexy-like symptoms	X						
Severe anaphylactic and anaphylactoid reactions			X	X	X	X	X
Changes in testosterone and prolactin levels				X			
Severe hepatic impairment			X	X	X	X	X
Withdrawal effects			X		X	X	X
Use in elderly and/or debilitated			X		X	X	X

Note: CNS = central nervous system.

effects were not observed; however, side inter- and intraindividual effects were observed, such that clinically important respiratory effects could not be ruled out. The effects of suvorexant on respiratory function should be considered if used in a patient with compromised respiratory function.[1]

Sleep paralysis, an inability to move or speak for up to several minutes during sleep-wake transitions, and hypnagogic/hypnopompic hallucinations, including vivid and disturbing perceptions by the patient, can occur with the use of suvorexant. These potential adverse events should be discussed with patients when prescribing suvorexant. Symptoms similar to mild cataplexy can also occur, including leg weakness lasting up to a few minutes occurring both at night and during the day.[1]

Suvorexant is undergoing Drug Enforcement Administration (DEA) review to determine the controlled substances schedule.[25] Abuse increases the risk of somnolence, daytime sleepiness, decreased reaction time, and impaired driving skills. In abuse liability studies, suvorexant produced effects similar to zolpidem on subjective ratings of "drug liking" and other measures of subjective drug effects. No evidence of physical dependence was observed in studies with prolonged use, and no withdrawal symptoms have been reported after suvorexant discontinuation.[1]

The safety and effectiveness of suvorexant have not been established in pediatric patients.[1]

Suvorexant is in Pregnancy Category C. It should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus. In animal models, suvorexant use in pregnancy was associated with decreased fetal body weight, but there was no evidence of teratogenicity.[1]

Suvorexant and the hydroxyl-suvorexant metabolite were excreted in rat milk and in higher concentrations than were observed in maternal plasma. It is not known whether suvorexant is secreted in human milk; however, caution is advised if suvorexant is administered to a breast-feeding woman.[1]

Cautions with the use of nonbenzodiazepine sedative hypnotics in special populations are summarized in **Table 3**.

ADVERSE REACTIONS

The most common adverse reaction associated with suvorexant is somnolence (reported in 7% of patients treated with suvorexant vs 3% of patients treated with placebo).[1] Other adverse effects reported in at least 2% of suvorexant-treated patients included headache (7%); dizziness (3%); and abnormal dreams, cough, diarrhea, dry mouth, and upper respiratory tract infection (all 2%).[1] Somnolence occurred more frequently in females than males (8% vs 3%), as did headache, abnormal dreams, dry mouth, cough, and upper respiratory tract infection.[1]

DRUG INTERACTIONS

Caution is advised if suvorexant is coadministered with other CNS depressant medications. Concurrent alcohol ingestion should be avoided.[1]

Coadministration of suvorexant with strong CYP3A inhibitors (eg, ketoconazole, itraconazole, posaconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, boceprevir, telaprevir, telithromycin, conivaptan) is not recommended. A reduced dose of suvorexant 5 mg is recommended in patients receiving moderate CYP3A inhibitors (eg, amprenavir, aprepitant, atazanavir, ciprofloxacin, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, imatinib, verapamil). The dose can be increased to 10 mg if necessary.[1]

Suvorexant exposure is substantially reduced, potentially resulting in reduced efficacy, if suvorexant is administered with strong CYP3A inducers (eg, rifampin, carbamazepine, phenytoin).[1]

Slightly increased digoxin levels were observed with digoxin and suvorexant coadministration because of inhibition of intestinal P-glycoprotein. Digoxin concentrations should be monitored with coadministration.[1]

Clinically important interactions were not observed between suvorexant and midazolam, warfarin, or a combined ethinyl estradiol/norgestimate oral contraceptive.[1]

RECOMMENDED MONITORING

No specific laboratory monitoring has been reported in clinical trials. Patients should be assessed for response and adverse events.

DOSING

The recommended dose is 10 mg taken no more than once per night and within 30 minutes of going to bed when at least 7 hours remain before the planned time of awakening. The time to effect may be delayed if taken with food or shortly after a meal. If the 10 mg dose is well tolerated but not effective, the dose may be increased. The maximum dose is 20 mg once daily. The lowest effective dose should be used.[1]

Table 3. Use of nonbenzodiazepine sedative hypnotics in special populations[1-7]

Population	Suvorexant	Doxepin	Eszopiclone	Ramelteon	Zaleplon	Zolpidem
Pregnancy	Category C; consider risk versus benefit	Category C; consider risk versus benefit	Category C; consider risk versus benefit	Category C; consider risk versus benefit	Category C; not recommended	Category C; consider risk versus benefit
Breast-feeding mothers	Caution	Caution	Unknown	Caution	Not recommended	Caution
Pediatric	Safety and effectiveness not established	Safety and effectiveness not established	Safety and effectiveness not established	Safety and effectiveness not established	Safety and effectiveness not established	Not recommended
Geriatric	No unique precautions	Reduce dose	Exposure increased; reduce dose	No unique precautions	Reduce dose	Reduce dose
Compromised respiratory function	Significant effects not observed; use with caution	Avoid in severe sleep apnea	Significant effects not observed; use with caution	Significant effects not observed; avoid in severe obstructive sleep apnea	Significant effects not observed; use with caution	Respiratory depression observed; use with caution
Hepatic impairment	Not recommended in severe impairment	Reduce dose	Caution; reduce dose in severe impairment	Caution in moderate impairment; avoid in severe impairment	Reduce dose in mild to moderate impairment; avoid in severe impairment	Reduce dose
Renal impairment	No dosage adjustment required	No dosage adjustment required	No dosage adjustment required	No dosage adjustment required	No dose adjustment required	No dose adjustment required
Gender	Increased exposure in females; caution with dose increase	No unique precautions	No unique precaution	No unique precautions	No unique precautions	Increased exposure in females; reduce dose

Table 4. Recommended dosage and administration for the nonbenzodiazepine sedative hypnotics[1-7]

	Recommended dose	Maximum dose	Dose adjustments in special populations
Suvorexant	10 mg once daily within 30 minutes of going to bed	20 mg once daily	With moderate CYP3A inhibitors, the recommended dose is 5 mg and the maximum dose is 10 mg. Not recommended in patients requiring treatment with a strong CYP3A inhibitor
Doxepin	3 to 6 mg within 30 minutes of going to bed	6 mg/day	Recommended starting dose is 3 mg in the elderly and those with hepatic impairment
Eszopiclone	1 mg immediately before bedtime	3 mg once daily	Not to exceed 2 mg in the elderly or debilitated, in patients with severe hepatic impairment, or with coadministration of potent CYP3A4 inhibitors
Ramelteon	8 mg within 30 minutes of going to bed	8 mg per day	None
Zaleplon	5 to 10 mg immediately before bedtime	20 mg once daily	In the elderly or debilitated, the recommended dose is 5 mg and maximum dose is 10 mg. In mild to moderate hepatic impairment, the recommended dose is 5 mg. With cimetidine, the initial dose is 5 mg.
Zolpidem extended release	6.25 mg for women and 6.25 or 12.5 mg for men immediately before bedtime	12.5 mg once daily	Recommended dose is 6.25 mg for the elderly and those with hepatic impairment.
Zolpidem tablets	5 mg for women and 5 to 10 mg for men immediately before bedtime	10 mg once daily	Recommended dose is 5 mg in the elderly and debilitated, and those with hepatic impairment.

Suvorexant exposure is increased in obese patients compared with nonobese patients and in women compared with men. The potential for increased adverse effects should be considered, particularly in obese women, prior to increasing the dose.[1]

When used with moderate CYP3A inhibitors, the recommended dose of suvorexant is 5 mg, and the dose generally should not exceed 10 mg. Use with strong CYP3A inhibitors is not recommended.[1]

Comparative dosages for the nonbenzodiazepine sedative hypnotics are summarized in **Table 4**.

PRODUCT AVAILABILITY

Suvorexant received FDA approval on August 13, 2014.[25] It is available as 5, 10, 15, and 20 mg film-coated tablets. The tablets should be stored in the original package until use in order to protect from light and moisture. Suvorexant tablets should be stored at room temperature (20°C to 25°C [68°F to 77°F]), with excursions permitted to 15°C to 30°C (59°F to 86°F).[1] Suvorexant is available in unit-of-use blisters of 30.[1] Availability of the nonbenzodiazepine sedative hypnotics are summarized in **Table 5**.

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS)

No REMS was required for suvorexant approval and no postmarketing studies were required under the conditions of approval.[25]

Suvorexant is currently under DEA review to determine its controlled substance status.[25]

CONCLUSION

Suvorexant is an orexin receptor antagonist that modestly reduced the TSO, increased TST, and reduced WASO in patients with primary insomnia. It offers an additional option for the therapy of insomnia with a unique mechanism of action. Head-to-head studies with other treatments are lacking. The long half-life and delayed T_{max}, as well as reports of daytime sleepiness, next-day impairment, sleep paralysis,

Table 5. Product availability for the nonbenzodiazepine sedative hypnotics[1-7,25-27]

	How available	Generic available	Controlled substance
Suvorexant	Tablets: 5, 10, 15, 20 mg	No	Yes, decision by the DEA is pending
Doxepin	Tablets: 3, 6 mg	No	No
Eszopiclone	Tablets: 1, 2, 3 mg	Yes	Yes, CIV
Ramelteon	Tablets: 8 mg	No	No
Zaleplon	Capsules: 5, 10 mg	Yes	Yes, CIV
Zolpidem	Tablets: 5, 10 mg Sublingual tablets: 1.75, 3.5, 5, 10 mg Oral spray: 5 mg/actuation	Tablets: yes Sublingual tablets: no Oral spray: no	Yes, CIV
Zolpidem extended-release	Extended-release tablets: 6.25, 12.5 mg	Yes	Yes, CIV

Note: CIV = Schedule IV; DEA = Drug Enforcement Administration.

hallucinations, and complex sleep behaviors within the clinical trial setting are to be considered. Additional adverse effect data, particularly at the approved lower dose, are necessary to further define its place in therapy.

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