# Suvorexant (Belsomra®)

## National Drug Monograph
## October 2015

**VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives**

*The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.*

## FDA Approval Information[1-4]

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| **Description/Mechanism of Action** | Belsomra (suvorexant) is a first-in-class orexin receptor antagonist. It is a CNS depressant and blocks the binding of wake-promoting neuropeptides orexin A and orexin B to the two orexin receptors (OX1R and OX2R) thus, altering the signaling (action) of orexin in the brain and suppressing the sleep-wake drive. |
| **Indication(s) Under Review in this document (may include off label)** | Treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance. |
| **Dosage Form(s) Under Review** | Tablets (round, film-coated): 5 (yellow), 10 (green), 15 (white), and 20 mg (white)<br>Suvorexant is a Schedule IV controlled-substance. |
| **REMS** | ☐ REMS ☒ No REMS ☐ Postmarketing Requirements |
| **Pregnancy** | Category C: Based on animal data, may cause fetal harm. |

## Executive Summary

Efficacy[1-3,5-8]

- Three Phase III studies evaluating a range of suvorexant doses in adult patients with insomnia characterized by difficulty falling asleep (latency) and/or staying asleep (maintenance) provided both objective and subjective evidence for efficacy for doses of 15mg and greater compared to placebo.
- Efficacy for measures of sleep latency (subjective total sleep onset; (sTSO) and objective latency of persistent sleep; (LPS) and sleep maintenance (subjective total sleep time; (sTST) and objective wake after sleep onset; (WASO) was maintained for three months with suvorexant high dose (20-40mg) and low dose (15-30mg).
- Sleep Maintenance: Based on two pooled Phase III trials (3 months in duration), suvorexant high dose compared to placebo at month 3 added ~ 22 minutes of sTST ($p<0.001$) and reduced WASO by 26 minutes ($p<0.001$). Suvorexant low dose compared to placebo added 16 minutes of sTST ($p<0.001$), and reduced WASO by 23 minutes at month 3, ($p<0.001$).
- Sleep Latency: Based on two pooled Phase III trials (3 months in duration), suvorexant high dose compared to placebo decreased sTSO by ~11 minutes, ($p<0.001$) and LPS by 6 minutes at month 3, ($p<0.05$). Suvorexant low dose compared to placebo decreased sTSO by 6 minutes ($p<0.01$) and decreased LPS by ~5 minutes at month 3, (p=NS).
- Efficacy for the 10mg suvorexant was determined by the exposure/response analysis from two Phase III studies and a Phase II dose finding study. The longest exposure to the 10 mg dose was in a phase II study, in which 62 non-elderly patients (<65 years of age) were exposed for one month. At 1 month, suvorexant 10mg reduced WASO and LPS (secondary endpoints) by 21 minutes ($p\leq 0.001$) and 2 minutes compared to placebo, (p=NS). Suvorexant 20mg was used longest by 20 patients in < 9 month trial.
- Suvorexant exposure is higher in women and obese patients defined as BMI >30kg/$m^2$.
- The concentration at 9 hours post-dose in elderly patients is ~15% greater than that in non-elderly adults. However, no meaningful differences in effectiveness were observed between patients ≥ 65 years and younger patients at the recommended doses.
- Due to the long half-life of 12 hours, suvorexant is a better option to consider in selective patients

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| | for sleep maintenance insomnia versus sleep initiation. |
| Safety[1-3,7, 9-10] | • The incidence of adverse effects is dose-related.<br>• In pooled data from 3-month Phase III trials and the first 3 months of a 12 month Phase III trial, the most common adverse events (≥ 2% greater than placebo) with high dose suvorexant was somnolence: 10.7%, (95% CI 11, 18); NNH 13.<br>• In pooled data from 3-month Phase III trials and the first 3 months of a 12 month Phase III trial, the most common adverse events (≥ 2% greater than placebo) with low dose suvorexant was somnolence 6.7%, (95% CI 17, 82); NNH 28.<br>• The incidence of somnolence with suvorexant 10 mg was 1.6% compared to 0.4% with placebo during a one year trial in patients with primary insomnia. In a trial with 22 healthy men (age 18-45 years), the incidence of somnolence the morning after evening administration was 4.5% vs. 0% with 10mg suvorexant compared to placebo.<br>• No discontinuation of suvorexant 10mg due to an adverse event in a Phase II trial was seen at one month (n=62). In other trials, the incidence of discontinuation due to an adverse reaction with suvorexant 15mg or 20mg was 3% compared to 5% placebo.<br>• The risk of next-day impairment, including impaired driving, is increased if suvorexant is taken with less than a full night of sleep remaining, a higher than recommended dose is taken, co-administered with other CNS depressants, or co-administered with other drugs that increase blood levels of suvorexant.<br>• No meaningful differences in safety were observed between patients 65 years and over and younger patients at the recommended doses to date.<br>• In completed clinical trials, there was no evidence for physical dependence with prolonged use. It is not associated with clinically meaningful rebound insomnia or withdrawal symptoms after discontinuation.<br>• No clinically significant respiratory depression in mild-to-moderate obstructive sleep apnea (OSA) and mild-to-moderate chronic obstructive pulmonary disease (COPD).<br>• Increased risk of suicidal ideation appears to be dose-related.<br>• Suvorexant was assessed for abuse liability with 40, 80, and 150 mg doses versus placebo, and zolpidem 15 and 30mg in recreational drug abusers. The effects of suvorexant and zolpidem were similar in the primary endpoint of "drug-liking" on a Visual Analogue Scale but zolpidem showed greater abuse liability in all other studied categories.<br>• No cases of severe cataplexy, although some reports of "weakness" were reported which might be considered mild cataplexy. The risk increases with higher doses. |
| | • *CNS Depressant Effects:* All CNS depressants can impair daytime wakefulness. Patients should be monitored for somnolence and CNS depressant effects. Impairment can occur in the absence of symptoms and may not be reliably detected by ordinary clinical exam. The CNS depressant effects may persist in some patients for up to several days after discontinuation.<br>o *Driving and Next-Day Impairment:* Suvorexant can impair driving skills and may increase the risk of falling asleep while driving. Impaired driving performance in both male and females occurred when the 20mg dose was taken. Because of individual variation in sensitivity to the drug, patients taking suvorexant especially those using the 20 mg dose should be cautioned against next-day driving and other activities requiring full mental alertness. Drivers poorly predict their own driving impairment so even at dose of 10mg, there is still a chance of driving impairment.<br>• *Concomitant Medications:* Co-administration with other CNS depressants (e.g., benzodiazepines, opioids, alcohol) increases the risk of CNS depression. Patients should be advised not to consume alcohol in combination with suvorexant due to the additive psychomotor impairment. Dosage adjustments of suvorexant and of concomitant CNS depressants may be necessary when administered together. Suvorexant is not recommended for use with strong CYP3A inhibitors and 5mg is the recommended dose when used with moderate CYP3A inhibitors. The use of suvorexant with other drugs to treat insomnia is not recommended.<br>• *Abnormal Thinking and Behavioral Changes:* Discontinuation of suvorexant is advised for patients that experience any complex sleep behavior (e.g., sleep-driving, preparing and eating |

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| | food, making phone calls).<br>• *Contraindication:* Suvorexant is contraindicated in patients with narcolepsy. |
| Potential Impact | • Suvorexant promotes a more "physiological sleep" unlike the other available agents used for the treatment of insomnia.<br>• Suvorexant has the indication for treatment of sleep onset and/or sleep maintenance, but due to its long-half life, the primary impact would be for sleep maintenance type of sleep disorders.<br>• Patient convenience:<br>o Once daily dosing but it is recommended to be taken within 30 minutes of going to bed, with at least 7 hours remaining before the planned time of awakening.<br>o Suvorexant does not appear to produce physical dependence or withdrawal. |

## Background

**Purpose for review**

Recent FDA approval
Issues to be determined:
√ Does the evidence show that suvorexant is effective as an agent for sleep maintenance and sleep onset?
√ Does suvorexant offer advantages over current VA National Formulary (VANF) agents?
√ What are the most appropriate patients for treatment with suvorexant?
√ Are there safety concerns in the Veteran population that may not have been addressed in the clinical trials?
√ What additional safety issues need to be considered with use of suvorexant?
√ Does suvorexant have specific characteristics best managed by the non-formulary process or criteria for use?

**Other therapeutic options**

| Formulary Alternatives (for sleep maintenance) | Other Considerations |
|---|---|
| **Temazepam** | Benzodiazepine (intermediate-acting); mean half-life~ 8 hours, potential for tolerance and dependence; associated with other CNS related adverse events; morning sedation and cognitive hangover effects, abuse potential, and rebound insomnia on withdrawal. Scheduled C-IV, indicated for short term treatment of insomnia. |
| **Zolpidem IR (not FDA approved for sleep maintenance)** | Mean half-life 1.6 hours; Scheduled C-IV; Recommended dose is 5mg for women and 5 or 10mg for men, immediately before bedtime with at least 7-8 hours remaining before the planned time of awakening. Recommended lower dose in geriatric patients and patients with hepatic impairment with recommended dose is 5 mg for men and women. CNS depressant effects; abuse and dependence potential; next-day impairment; recommended not to drive a car or do things that require clear thinking the day after taking dose, available generic. |
| **Non-formulary Alternative (if applicable)** | **Other Considerations** |
| **Zolpidem Extended Release** | Mean half-life 2.8 hours; Scheduled C-IV; recommended lower dose in women and in patients with hepatic impairment; administered immediately before bedtime with at least 7-8 hours remaining before planned time of awakening; CNS depressant effects; abuse and dependence potential; next-day impairment; recommended not to drive a car or do things that require clear thinking the day after taking dose. |
| **Eszopiclone** | Half-life 5-7 hours; may extend to 9 hours in older adults. Schedule C-IV. Moderate potential for drug-drug interactions (metabolized in part by CYP3A4). Unpleasant metallic taste; available generic. |
| **Low dose doxepin** | Tricyclic antidepressant. Indication for sleep maintenance only. No significant next-day residual effects. |

## Efficacy (FDA Approved Indications) [1-3,5-8,11]

### Literature Search Summary

A literature search was performed on PubMed/Medline (2010 to August 2015) using the search terms suvorexant, orexin receptor antagonism, and Belsomra. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles and the manufacturer's AMCP dossier and transcripts on

FDA web site were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

**Review of Efficacy**
Current available evidence is high quality for the use of suvorexant in patients with insomnia although the pivotal trials were conducted and funded by the manufacturer of suvorexant. (Refer to Appendix A).

The efficacy of suvorexant in patients with primary insomnia was investigated in three phase III clinical trials. Two of the trials were randomized, double-blind, placebo-controlled, parallel-group of 3 months in duration including objective and subjective assessments with an optional 3-month double-blind extension in Trial 1. Each trial enrolled adult patients (18-64 years) and elderly patients (≥ 65 years of age) who met DSM-IV-TR criteria for primary insomnia and a score ≥25 on the Mini Mental State Examinations (MMSE).

Eligibility for inclusion for both trials was assessed with subjective sleep measures in all patients and approximately 75% of the patients also underwent objective evaluation using polysomnography (PSG). Patients with only subjective sleep assessment via an electronic sleep diary questionnaire, recruited exclusively from Japan (Trial 1) and Asia Pacific (Trial 2), were randomized if the total sleep time (sTST) was < 6.5 hours and the time to sleep onset (sTSO) was ≥ 30 minutes for ≥4 of the 7 nights during screening. Patients screened objectively were randomized if the sleep latency of persistent sleep (LPS) was > 20 minutes and the mean wakefulness after persistent sleep onset (WASO) was ≥ 60 minutes. Patients in the PSG group were excluded if the apnea-hypopnea index or a periodic leg movement arousal index was > 10 (nonelderly) or < 15 in the elderly. Two doses were evaluated in each age group: high dose (HD), defined as 40 mg or 30 mg for adults, and low dose (LD), defined as 20 mg or 15 mg for the elderly. Randomization was to LD, HD, or placebo in a 2:3:3 ratio, respectively and a 1:1:1 ratio in those patients that only had subjective assessments. A prespecified multiplicity strategy was used for the two indications (sleep maintenance and onset) but differed between the two trials. The study was powered for high dose objective sleep maintenance endpoints.

Patient characteristics and baseline symptom severity were similar among treatment groups in both trials. Trial 1 randomized 1021 patients (mean age 56 years) of which 42% (n=429) were elderly. For Trial 2, 1019 patients (mean age 57, 41% elderly) were randomized. The percentage of females enrolled in Trial 1 and 2 were 63% and 66%, respectively. Obese patients (>30 $kg/m^2$) made up 12% and 15% of the total population in Trial 1 and 2; respectively. In all groups, baseline score for all patients was 16 on the Insomnia Severity Index (ISI 0-28 scale).

The primary efficacy endpoints for suvorexant 40 mg and 30 mg were a change from baseline at months 1 and 3 for subjective and objective measures of sleep maintenance (sTST, WASO) and sleep onset (sTSO, LPS), respectively. Secondary end points were the same variables at week 1 for subjective measures and at night 1 for objective measures. These variables were assessed for suvorexant 20 mg and 15 mg as secondary endpoints for Trial 1 and exploratory end points for Trial 2. Other diary end points for both trials were considered exploratory endpoints and included the following: number of awakenings (sNAW); wake time after sleep onset (sWASO); sleep quality (sQAL); and refreshed upon awakening (sFRESH).

Responder rating scales (exploratory endpoints for both trials) included: Insomnia Severity Index (ISI); Clinical Global Impression-Severity scale (CGI-S); Patient Global Impression-Severity scale (PGI-S) (Trial 2 only); Clinical Global Impression-Improvement scale (CGI-I); Patient Global Impression-Improvement scale (PGI-I).

Results: (Refer to Table 1 for details)

**Sleep Maintenance:** Primary Endpoints (sTST, WASO)
- High dose suvorexant vs. placebo was statistically significant for both primary endpoints at all time points; week1/night1, month 1, and month 3 in both trials, (all p <0.001)
- Low dose suvorexant vs. placebo was statistically significant for both primary endpoints at all time points in both trials. The NNT to achieve 15% improvement in mean sTST with LD suvorexant based on pooled results from Trials 1 and 2 is 9, 8, and 13 at week 1, month 1, and month 3, respectively. (Refer to Table 2 for details)

**Sleep Latency: (sTSO, LPS)**

- High dose suvorexant vs. placebo was statistically significant in improving sleep latency at all time points in both trials except LPS at month 3 in Trial 2.
- Low dose suvorexant vs. placebo was statistically superior for LPS at all time points in Trial 1 except month 3 in Trial 2. For sTSO, LD suvorexant improved at all time points however beyond month 1, the differences observed at month 3 were not tremendously different than month 1. The p values for sTSO were nominally positive compared to placebo ($p < 0.04$) in both trials at month 3. It should be noted that because the study was underpowered for sleep latency outcomes, non-significant findings at some time points for LD is not unexpected. The FDA did rule that because the objective findings for sleep latency (LPS) were positive in Trial 1 and in combination with two nominally subjective sTSO findings in Trial 1 and 2 at month 3, there was sufficient evidence to support the efficacy of low doses for sleep latency. The NNT to achieve 15% improvement in mean sTSO with LD suvorexant compared to placebo based on pooled results from Trial 1 and 2 is 8, 12, and 26 at week 1, month 1, and month 3, respectively. (Refer to Table 2)

Secondary Outcomes:

High dose suvorexant vs. placebo

- sWASO was statistical significant throughout all time points in both trials.
- sQUAL (patient's perceptions of sleep) significantly improved in Trial 1 week 1 ($p < 0.001$), month 1 ($p < 0.001$), and month 3 ($p < 0.05$). Significant results for sQUAL were also seen for all assessment times in Trial 2.
- sFRESH was significantly improved with for both week 1, and month 1 in both trials (both $p<0.01$) but only month 3 in Trial 2, ($p<0.01$).
- sNAW was not statistically different at any time points in both trials.
- Clinical and patient global impression scales statistically improved at all time points in both trials.

Low dose suvorexant vs. placebo

- sWASO statistically improved throughout all time points except at month 1, and month 3 in Trial 1 and week 1 in Trial 2.
- sQUAL was statistical significant throughout all time points except at month 3 in Trial 1.
- sFRESH was statistical significant for all time points except at month 3 in Trial 1 and week 1 in Trial 2.
- sNAW was not significant at any time points in Trial 1 or Trial 2.
- Clinical and patient global impression scales improved at all time points in both trials.

Table 1[5]: Two Phase 3 Studies: Primary Sleep Maintenance and Sleep Onset Endpoints

| | Mean change from baseline (95% CI)/p | | | | | |
|---|---|---|---|---|---|---|
| **Sleep Maintenance** | | | | | | |
| | Trial 1 | | | Trial 2 | | |
| *Objective: WASO, min* | | | | | | |
| | Night 1(Objective) Week 1 (Subjective) | Month 1 | Month 3 | Night 1 | Month 1 | Month 3 |
| HD vs. Placebo | -38.4 (-45.5, -32.3) <0.00001 | -26.3 (-33.5, -19.2) <0.00001 | -22.9 (30.3, -15.4) 0.00001 | -42.0 (-48.6, -35.3) <0.00001 | -29.4 (-36.6, -22.3) <0.00001 | -29.4 (-36.7, -22.1) <0.00001 |
| LD vs. Placebo | -32.5 (-39.3, -25.7) <0.00001 | -26.4 (-34.3, -18.4) <0.00001 | -16.6 (-24.8, -8.3) 0.000009 | -37.0 (-45.1,-28.8) <0.00001 | -24.1(-33.0,-15.3) 0.00001 | -31.1 (-40.1, -22.2) 0.000009 |
| *Subjective: sTST, min* | | | | | | |
| HD vs. Placebo | 21.4 (15.5, 27.4) <0.00001 | 19.6 (12.0, 27.1) <0.00001 | 19.7 (11.9, 27.6) <0.00001 | 26.4 (19.8, 33.1) <0.00001 | 26.3 (18.3,34.3) <0.00001 | 25.1 (16.0, 34.2) <0.00001 |
| LD vs. Placebo | 13.6 (6.9, 20.2) 0.00007 | 16.3 (7.9, 24.8) 0.00016 | 10.7 (1.9, 19.5) 0.017 | 16.8 (9.1, 24.5) 0.00002 | 20.9 (11.7, 30.2) <0.00001 | 22.1 (11.5, 32.6) 0.00004 |
| **Sleep Onset** | | | | | | |
| *Objective: LPS, min* | | | | | | |
| HD vs. Placebo | -10.3 (-15.0, -5.5) 0.00002 | -11.2 (-16.3, -6.1) 0.00002 | -9.4 (-14.6, -4.3) 0.0004 | -21.7 (-28.6, -14.9) <0.00001 | -12.1 (-17.8, -6.4) 0.00004 | -3.6 (-10.1, 2.8) 0.27 |
| LD vs. Placebo | -9.6 (-14.9, -4.3) 0.0004 | -10.3 (-16.0, -4.6) 0.0004 | -8.1 (-13.8, -2.3) 0.0061 | -12.4 (-20.7, -4.0) 0.004 | -7.8 (-15.0, -.7) 0.03 | -0.3 (-8.3, 7.6) 0.93 |
| *Subjective: sTSO, min* | | | | | | |
| HD vs. Placebo | -5.7 (-9.7, -1.6) 0.0061 | -7.4 (-12.3, -2.5) 0.003 | -8.4 (-12.8, -4.0) 0.0002 | -13.1 (-17.7, -8.4) <0.00001 | -12.8 (-18.8, -6.9) 0.00003 | -13.2 (-19.4, -7.0) 0.00003 |
| LD vs. Placebo | -5.6 (-10.2, -1.1) | -5.4 (-10.9, .0) | -5.2 (-10.2, -.3) | -7.5 (-12.9, -2.2) | -6.9 (-13.7, -.0) | -7.6 (-14.7, -.4) |

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| | 0.016 | 0.052 | 0.04 | 0.006 | 0.05 | 0.04 |

HD=Suvorexant 20/40mg; LD= Suvorexant 15/30mg; WASO= Wake After Sleep Onset; sTST=Subjective Total Sleep Time; LPS= Latency to onset of persistent sleep; sTSO= Subjective Total Sleep Onset

Table 2[7]: NNT for ISI, sTST, sWASO and sTSO with LD Suvorexant: Trial 1 and Trial 2 (pooled results)

| Measure | Time Point | Suvorexant 15/20mg vs. placebo NNT (95% CI) |
|---|---|---|
| ≥ 6 point improvement in ISI total score | Month 1 | 10 (7-9) |
| | Month 3 | 8 (6-14) |
| ≥ 15% improvement in mean sTST (sleep maintenance) | Week 1 | 9 (6-15) |
| | Month 1 | 8 (6-14) |
| | Month 3 | 13 (7-46) |
| ≥ 15% improvement in mean sWASO (sleep maintenance) | Week 1 | 12(8-39) |
| | Month 1 | 12 (8-37) |
| | Month 3 | 16 (9-102) |
| ≥ 15% improvement in mean sTSO (sleep latency) | Week 1 | 8 (6-14) |
| | Month 1 | 12 (7-34) |
| | Month 3 | 26 (NS) |

ISI, Insomnia Severity Index; sTST subjective total sleep time; sWASO, subjective wake time after sleep onset; sTSO, subjective time to sleep onset; CI, confidence interval; NNT, number needed to treat; NS, not significant.

Herring[5] et al. conducted a phase II dose-finding two-period cross-over study examining the efficacy of suvorexant 10 mg, 20 mg, 40 mg, and 80 mg. A total of 254 adults with primary insomnia were randomized with ~ 60 patients in each dose arm. Co-primary efficacy end points were objective sleep efficiency (defined as TST/time in bed in minutes [fixed at 480 for this study] multiplied by 100) on night 1 and end of week 4. Secondary endpoints were WASO and LPS. All suvorexant doses showed significant improvement in sleep efficiency vs. placebo

All doses compared to placebo significantly reduced WASO at both time points, ($p \leq 0.001$). The multiplicity strategy resulted in no dose being positive for LPS. However, when an analysis of LPS was performed between the first and second study periods to minimize the carryover effect) and applying the multiplicity testing strategy, the 40 mg and 80 mg dose significantly improved LPS when compared to placebo at night 1, while the 20 mg resulted in a significant improvement at week 4. The 10mg dose showed a significant improvement in objective sleep maintenance and for objective sleep latency when a post-hoc sensitivity analyses was performed. Many of the exploratory patient-reported outcomes including sTST, sTSO, sQUAL, sFRESH were negative for both the 10 mg and 20 mg doses at week 1 and 4 when compared to placebo but again, this study was not powered for those endpoints. Some evidence of subjective benefit was noted from the scores of insomnia severity index for all doses; however the p-values were not positive for suvorexant 10 mg. (Refer to Appendix B for more details.)

Long-Term Efficacy[8]:
A randomized, placebo-controlled, parallel group Phase III trial in 781 patients with primary insomnia (mean age 62) and a BMI > 30 kg/m2 in 23% of the total population was conducted to assess the safety and tolerability of suvorexant for up to year, while assessing the efficacy for sTST and TSO over the first month of treatment as secondary outcomes. Most patients were mild-to-moderate insomnia at baseline. Adult patients received suvorexant 40mg while elderly patients (≥65) received 30mg or placebo at a 2:1 ratio for 1-year with a subsequent 2-month randomized discontinuation phase in which patients on suvorexant either continued suvorexant or were abruptly switched to placebo. Patients on placebo remained on placebo. (Refer to Safety section for long term findings.)

Over the first month, suvorexant showed significant improvement in sTST ($p<0.0001$) and sTSO ($p= 0.0002$) compared to placebo. The improvements were maintained through the 1-year period. Suvorexant was better than placebo on all subjective sleep measures at month 1 and month 12, except for sNAW at month 1. Suvorexant was also better than placebo at both time points on the ISI, CGI-S, PGI-S, CGI-I, and PGI-I.

Summary of Efficacy:
When four double-blind, randomized, placebo-controlled trials evaluating suvorexant for primary insomnia were included in a meta-analysis[11], suvorexant was found to be superior to placebo, with regard to two primary efficacy

subjective outcomes: sTST (measure of sleep maintenance): WMD -20, (95% CI -25.01, -15.30), (1889 patients, 3 trials) and sTSO (measure of sleep latency): WMD -762; (95% CI -11.03, -4.21), (1889 patients, 3 trials). (Refer to Table 1 for specific outcomes with higher vs. lower doses of suvorexant.) The efficacy of suvorexant 10mg was determined by the exposure/response analysis from two Phase III studies and a Phase II dose finding study. The longest exposure to the 10 mg dose was in a phase 2 study, in which 62 non-elderly patients (<65 years of age) were exposed for one month.

## Potential Off-Label Use [12-13]

- No published studies at the time of this document were found using suvorexant in other off-label conditions. Other dual orexin receptor antagonists have been evaluated in painful diabetic neuropathy, migraine prophylaxis, and as an adjunctive therapy in major depressive disorder.

## Safety[1-3] (for more detailed information refer to the product package insert)

| | **Comments** |
|---|---|
| **Boxed Warning** | • None |
| **Contraindications** | • Do not use in patients with narcolepsy. |
| **Warnings/Precautions** | • Daytime somnolence: Risk of impaired alertness and motor coordination, including impaired driving can occur; the risk increases with dose escalation. Caution patients taking 20mg against next-day driving and other activities requiring complete mental alertness. The risk of impairment can occur even when fully awake.<br>• Need to evaluate for co-morbid diagnoses: Reevaluate if insomnia persists after 7 to 10 days of treatment.<br>• Nighttime "sleep-driving" and other complex behaviors while out of bed and not fully awake can occur. The risk increases with dose escalation, with use of CNS depressants, and with alcohol.<br>• Depression: Worsening of depression or suicidal thinking may occur. The risk increases with dose escalation.<br>• Compromised respiratory function: The effect on respiratory function should be considered.<br>• Sleep paralysis, hypnagogic/hypnopompic hallucinations, and cataplexy-like symptoms: The risk increases with dose escalation. |

**Safety Considerations**

Adverse effects are strongly dose-related. Key safety issues include:

- Daytime somnolence/excessive daytime sleepiness; driving impairment
  - The incidence of somnolence is dose related. In the dose ranging study, the incidence of somnolence was 0.4% for placebo, 1.6% for 10 mg, and 4.9% for 20 mg suvorexant.
- Excessive daytime sleepiness (EDS)
  - In the 3 month trial, the incidence of EDS was 0.2%, 0.6% and 1.1% (n=14) for placebo, low dose (LD) and high dose (HD) suvorexant, respectively. Ten of the fourteen HD patients (71%) discontinued suvorexant due to EDS. In the 12 month trial, 11 suvorexant HD (0.9%), and 2 placebo (0.2%) patients discontinued due to EDS.
  - Driving impairment: Next day suvorexant blood levels in adults after nighttime administration with 15 mg dose overlaps with blood levels from the 20 mg dose causing driving impairment in the formal driving study. Drivers poorly predict their own driving impairment. Remember evaluating the average impairment of all patients is not sensitive to clinically important impairment in individuals. Drivers may be impaired but not know it. Patients should be cautioned even with the 10 mg dose and advised not to drive the next morning.
- Suicide risk
  - The risk of suicidal ideation was evident mainly with the high dose. At doses 30-40mg, there was a 7-fold increase in suicidal ideation vs. placebo. For low dose suvorexant (15-20 mg), an insufficient number of events are available to determine the relative risk with confidence. Suvorexant studies generally excluded patients taking antidepressants and patients with active depressive symptoms or suicidal ideation. There is no experience with the use of this agent in this population and an effort to identify patients with suicidal ideation before and while being treated with suvorexant should be made.

- Unconscious nighttime activity
  - Two cases have been reported; one case with suvorexant 40 mg and one case with 30 mg suvorexant. No cases with placebo were reported. It is not clear that these events represent a drug-related risk.
- Narcolepsy-like events other than daytime somnolence: cataplexy, hypnagogic hallucinations, and sleep paralysis
  - Sleep paralysis and hypnagogic/hynopompic hallucinations appears to be dose-related. It is not likely to cause physical harm but potentially very distressing to patients. Again, using the lowest dose effective is highly recommended.
- Abuse:
  - In human abuse potential study, the "drug like" of suvorexant was similar to that of zolpidem. In clinical trials, euphoria and other adverse events suggestive of abuse were observed infrequently**.**

## SAFETY[1-3, 7-8, 10-11]

**Long-Term:**

During 1-year of treatment, more serious adverse events were reported in the placebo group (6.6%) vs. the suvorexant group (5.2%). However, one or more drug-related adverse events occurred more often in the suvorexant group (34.9%) vs. the placebo group (20.5%), (95% CI 7.8, 20.6). The three most common adverse events with suvorexant vs. placebo at one year were somnolence13.2% vs 2.7%, (95% CI 6.8, 14.1), fatigue 6.5% vs.1.9%, (95% CI 1.6, 7.4) and dry mouth 5.0% vs. 1.6%, (95% CI 0.7, 5.9), respectively. (Refer to Table 3 for the NNH). Discontinuation due to drug-related adverse events was slightly higher in the suvorexant group at 8.3% compared to 4.7% with placebo, (95% CI -1.5, 7.4). The adverse event with the highest incidence of discontinuation compared to placebo was somnolence (4% vs 1%), respectively. The incidence of excessive daytime sleepiness defined as a more persistent daytime sleepiness than typical next-day residual somnolence was 2.5% (n=13) compared to 0.8% (n=2), (95% CI -0.5, 3.6) in the suvorexant vs. placebo groups, respectively.

Table 3[7]: Common adverse events* of LD and HD Suvorexant vs. placebo and NNH (pooled results)

| Adverse event | Suvorexant 15 or 20mg vs placebo NNH (95% CI) | Suvorexant 30 or 40mg vs placebo NNH (95% CI) |
|---|---|---|
| Somnolence | 28 (17-82) | 13 (11-18) |
| Headache | 74 (ns) | 158 (ns) |
| Dizziness | 469 (ns) | Rate lower than placebo |
| Abnormal dreams | 118 (ns) | 90 (48-769) |
| Diarrhea | 103 (ns) | 613 (ns) |
| Dry Mouth | 218 (ns) | 71 (39-361) |
| Nausea | Rate lower than for placebo | 189 (ns) |
| Fatigue | 211 (ns) | 49 (30-139) |
| Upper respiratory infection | 222 (ns) | 101 (ns) |

*≥2% incidence in LD Suvorexant and frequency greater for suvorexant than for placebo in Trial 1and 2 plus the first 3 months of long-term (12 month) Phase 3 trial ; CI, confidence interval; NNH, number needed to harm; ns, not significant; HD=Suvorexant 20/40mg; LD= Suvorexant 15/30mg

**Rebound Insomnia** (exploratory endpoint): No evidence of rebound was seen for any measure in patients during the first three nights of the discontinuation phase. No statistically significant differences were seen 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 proportion of patients with rebound insomnia on all comparison were numerically greater with return of symptoms similar in severity in the suvorexant-placebo group compared with the placebo-placebo group during the 2-month discontinuation phase, however most patients retained some degree of improvement during the 2-month discontinuation phase. Authors stated that the return of symptoms following suvorexant discontinuation could be a return of the underlying insomnia disorder, rebound or withdrawal effects, or a combination of all of these mechanisms. In a meta-analysis[11], with three combined trials (n=1486), the rebound insomnia measured by sTST at day 1-3 for switching suvorexant to placebo group versus switching placebo to placebo was RR 1.20, (95% CI 1.10, 1.40); p=0.005; NNH = 11.

**Withdrawal Symptoms** (exploratory endpoint): Using the Tyrer Withdrawal Symptom Questionnaire, there were no statistically significant differences observed between the suvorexant/suvorexant and suvorexant/placebo groups for the percent of patients with worsening of ≥3 symptoms during each of the first 3 nights or across the first 3 nights of the discontinuation phase. No evidence of withdrawal symptoms was noted at day 1, day 2, day 3, or days 1-3 when a meta-analysis[11] was conducted of the three combined trials.

**Next-day residual:** In a randomized, double-blind, placebo-controlled, 4-period crossover PSG study conducted in healthy young men (n=22), no evidence of next-day residual effect for suvorexant 10mg was seen on simple reaction time (SRT), choice reaction time (CRT), and digit symbol substitution test (DSST) evaluated at 10 hour post dose compared to placebo.

**Next-day daytime function:**
In a phase 1 study in which next-day (9 hour post dose) memory and balance were evaluated after a single dose of 40mg, there was a statistically significant decrease in word recall, and a statistically significant increase in body sway following a single dose of suvorexant 20 mg or 40 mg. Psychomotor performance measured by DSST showed no clear change from suvorexant. No increase incidence of falls was observed. The incidence of falls was essentially the same among all treatment groups in controlled trials. The falls that occurred in the drug-treated patients all appeared to have been related to identifiable non-drug related causes. The effect on memory also appears to be small and with uncertain clinical meaningfulness.

**Driving:**[1-3]
Two similar 4 period cross-over studies evaluating highway driving behaviors were conducted. One study evaluated the driving in 24 healthy subjects (> 65 years old) receiving 8 consecutive days of suvorexant 20 mg, 40 mg or placebo. ~~and~~ The other study evaluated driving in 28 healthy subjects (ages 21-64 year old) with suvorexant 15 mg, 30 mg or placebo for 8 consecutive days. Driving (one hour duration) was evaluated in the morning about 9 hours after nighttime dose, on day 2 and 9, after 8 days of dosing. Blood levels were measured at 11 hours after drug ingestion. The primary endpoint was the mean standard deviation of lane position (SDLP), a measure of the ability of the driver to maintain a constant position of the car in the driving lane. Zolpiclone 7.5mg was used as an active control. Because the FDA considers the mean SDLP not sensitive to clinically important impairment in individuals, a symmetry analysis was conducted and compared the proportion of patients that worsened by a threshold of 2.4cm (the level of impairment generally accepted as representing that of 0.05% blood ethanol) to the proportion that improved by that amount. A positive correlation between suvorexant blood level and SDLP impairment, on day 2 for both suvorexant 20 mg and 40 mg and on day 9 for suvorexant 40mg was observed although a clear cut-off blood level with no impairment was not noted. In the dose ranging study[6], suvorexant blood levels the morning after the 10 mg dose averaged about 0.2 to 0.3 µM and up to 0.4 µM in adult patients which raises some concern than even after the 10 mg dose, some adults might experience clinically meaningful driving impairment. Of note, the driving study in elderly was not positive by symmetry analysis for either dose at either day.

**Adverse Reactions**

Common adverse reactions

Trials > 3 months:
With suvorexant 15 mg or 20 mg, the most common adverse reaction (reported in ≥ 5% of patients and at least twice the placebo rate) was somnolence (suvorexant 7% vs. placebo 3%). Adverse events with an incidence ≥2% included headache, somnolence, and dizziness. The overall incidence of somnolence in treated patients was 11% for high dose vs. 7% in low dose.

Incidence (%) of Common Adverse Events, 3, 6 and 12 month controlled Trials

| | 3 month trials | | | 6 month | | 12 month | |
|---|---|---|---|---|---|---|---|
| Adverse Event | Placebo N=1025 | LD N=493 | HD N=1291 | Placebo N=767 | LD N=493 | Placebo N=1025 | HD N=1291 |
| Somnolence | 3 | 7 | 11 | 3 | 7 | 3 | 12 |
| Severe somnolence | 0.1 | 0.2 | 0.6 | | | | |
| >65 year old | 3 | 5 | 9 | | | | |
| < 65 year old | 3 | 8 | 12.5 | | | | |
| Men | 4 | 3 | 10 | | | | |
| Female | 2 | 8.5 | 11 | | | | |
| Headache | 6 | 7 | 7 | 6 | 8 | 7 | 8 |
| Fatigue | 2 | 2 | 4 | | | 2 | 5 |
| Dry Mouth | 1 | 2 | 3 | | | 2 | 3 |
| Abnormal Dreams | 1 | 2 | 2 | 1 | 2 | 1 | 3 |
| URI | 1 | 2 | 2 | | | 2 | 3 |
| Nausea | | | | | | 2 | 3 |
| Nightmares | | | | | | 1 | 2 |
| Diarrhea | | | | 1 | 2 | | |
| Cough | | | | 1 | 2 | | |

At doses of 15 mg or 20 mg (n=493), the incidence of somnolence was higher in females (9%) than in males (3%) and in adults (8%) vs. elderly (5%) although the elderly received a lower dose per protocol.

Incidence of Somnolence by BMI Categories:

| | Placebo | LD | HD |
|---|---|---|---|
| Non-Obese (BMI < 25) | 2.2% (10/449) | 7.4% (18/243) | 11.0% (56/509) |
| Over-weight (BMI 25-30) | 3.0% (12/405) | 7.2% (14/194) | 8.9% (49/548) |
| Obese (BMI >30) | 5.3% (9/170) | 1.8% (1/56) | 13.4 (31/232) |

The incidence of adverse effects (≥2% ) in women vs. men: headache, abnormal dreams, dry mouth, cough, and upper respiratory tract infection.

**Death/Serious adverse reactions**

Nonfatal serious adverse events were uncommon, with fewer serious adverse events in the suvorexant arms compared with placebo. There was one serious adverse event of suicidal ideation in one patient with a past history of suicidal ideation and remote history of suicide attempt taking 40 mg suvorexant.

Over 6 months of controlled trial data, 0.6% and 2.1% of suvorexant LD (n=493) and placebo (n=767) patients, respectively, experienced a serious adverse event. No single adverse event occurred more than once in the suvorexant LD group.

**Discontinuations due to adverse reactions**

Incidence of Discontinuation, Phase 3 studies:

| | Placebo | LD | HD |
|---|---|---|---|
| 0-3 months | 4.7% | 3.2% | 5.4% |
| 0-6 months | 5.2% | 3.2% | NA |
| 0-12 months | 6.0% | NA | 7.8% |

LD= low dose (15-20mg); HD=high dose (30-40 mg)

The incidence of discontinuation due to adverse events was dose dependent. Discontinuation was highest with suvorexant high dose compared to low dose and placebo, but the differences between treatment groups were small.

The leading causes of discontinuation in the 3 month trials in the low-dose group compared to placebo were somnolence (0.2% vs. 0.3%); fatigue (0.2% vs. 0); and nightmare (0.2% vs. 0). No individual adverse reaction led to discontinuation at an incidence ≥ 1%.

## Drug Interactions

### Drug-Drug Interactions[1,-3, 6, 8]

Consult the prescribing information prior to use of suvorexant for potential drug interactions.

- Suvorexant is a weak inhibitor of CYP3A and the intestinal P-glycoprotein (P-gp) transporter following consecutive multiple-dose administration. The major route of metabolism for suvorexant is CYP3A. Concomitant use of suvorexant with:
  - *Strong CYP3A Inhibitors* is not recommended: Exposure (AUC) of suvorexant is increased about 3-fold by strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, boceprevir, telaprevir).
  - *Moderate CYP3A Inhibitors:* the recommended dose of suvorexant is 5 mg and can be increased to 10 mg maximum if needed. Exposure of suvorexant is increase about 2-fold by moderate CYP3A inhibitors (e.g., ciprofloxacin, diltiazem, erythromycin fluconazole, grapefruit juice, verapamil). If 10mg dose is used, patients should refrain from driving the next day.
  - *Strong CYP3A Inducers* can substantially decrease suvorexant exposure. The efficacy of suvorexant may be reduced (e.g., rifampin, carbamazepine, phenytoin).
  - *Warfarin or oral contraceptives*: No clinical significant pharmacokinetic interactions were observed following the co-administration of suvorexant.
  - *CNS Depressants*: Dosage adjustment of suvorexant and/or the other CNS depressant may be necessary.
  - *Midazolam* (a sensitive CYP3A substrate): Midazolam levels may slightly increase with concomitant administration of suvorexant.
  - *Digoxin:* Digoxin levels may slightly increase with concomitant administration of suvorexant due to inhibition of intestinal P-gp. Digoxin concentrations should be monitored as clinically indicated.

**Drug-Lab Interactions**
In a dose ranging study, non-elderly patients treated with suvorexant for up to one month with various doses had a strongly dose-related increase in cholesterol levels (10mg:↑ 1.2 mg/dL; 20mg: ↑ 2.3mg/dL; 40mg, ↑3.1 mg/dL; and 80mg, ↑ 6mg/dL). Cholesterol levels were not measured in phase III studies. When using the recommended dose of 10mg no increased monitoring of cholesterol levels would be warranted.

For the three combined phase III studies, the incidence of a predefined reduction in absolute neutrophil count (ANC) to less than ≤ 37% of normal occurred in 1.0% (n=5/484) with suvorexant low dose (15-30 mg), 0.5% (n=6/1281) with higher doses (20-40mg), and 0.1% (n=1/1009) with placebo. Three patients had preexisting mild or moderate neutropenia. Five of the eleven suvorexant patients return to baseline laboratory tests were not documented. The lowest neutrophil count was 0.2 x $10^3$ cells/μL. The investigators noted that the low neutrophil count occurred sporadically over the course of treatment, without apparent worsening or infection. However, because follow-up testing did not occur for about half of the affected patients, neutropenia due to drug or chance is not known.

## Risk Evaluation:

As of October, 2015

| | **Comments** |
|---|---|
| Sentinel event advisories | • None |
| Look-alike/sound-alike error potentials | • Sources: ISMP, FDA, TJC |

| NME Drug Name | Lex-Comp | First DataBank | ISMP | Clinical Judgment |
|---|---|---|---|---|
| Suvorexant 5, 10 15, 20 mg tab | None | None | None | Suboxone Resuvo |
| Belsomra | None | None | None | Belviq Soma Unisom |

## Other Considerations

- Suvorexant needs to be dispensed with an FDA approved patient Medication Guide. Suvorexant is a controlled substance (Schedule-IV).
- Potential abuse of suvorexant was evaluated in a phase I randomized, double-blind, placebo and active comparator-controlled, 6 way crossover study. Single doses of suvorexant 40 mg, 80 mg, 150 mg and 2 doses of zolpidem (15 mg and 30 mg) in 73 recreational polydrug users were evaluated. Suvorexant showed greater abuse potential than placebo as measured by the Drug Liking VAS. Both suvorexant and zolpidem showed greater abuse potential than placebo on other positive measure of drug abuse potential.
- Suvorexant has not been compared to other drugs approved to treat insomnia, so differences in safety or effectiveness between suvorexant and other insomnia medications are not known.
- No information is available on switching patient to suvorexant from current hypnotic therapies.
- No information is available on the use of suvorexant in patients who fail to respond to current hypnotic therapies.
- All the efficacy and safety Phase III trials enrolled generally healthy patients. There is minimal data in concomitant disease or use with drugs commonly used in actual clinical population.

## Dosing and Administration

- Refer to Drug-Drug Interaction Section
- The recommended dose is 10 mg, taken no more than once per night and within 30 minutes of going to bed, with at least 7 hours remaining before the planned time of awakening. The maximum recommended dose is 20 mg once daily. However, due to inter-individual variation in both pharmacokinetics and pharmacodynamics, and with the potential of serious dose-related adverse effects, the lowest dose effective to treat an individual's symptoms should be used.
- An increased suvorexant exposure in women vs. men and in obese (>30 kg/m2) vs. non-obese patients has been noted. Approximately a doubling of suvorexant exposure in obese females vs. non-obese and a 20% increase in blood levels the morning after dosing at steady state has been shown. Knowing the increased exposure in these

populations, using doses higher than the initial starting dose of 10 mg warrants clinical judgment and shared patient-centric decision.
- Time to effect may be delayed if taken with or soon after a meal.

## Special Populations (Adults) [1-3]

| | Comments |
|---|---|
| **Elderly** | • The blood levels of suvorexant 9 hours post-dose were ~15% higher in elderly versus non-elderly patients from Phase 1 studies; however no dose-adjustment for age is recommended. |
| **Pregnancy** | • There are no adequate and well-controlled studies in pregnant women. Suvorexant should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. |
| **Lactation** | • No data is available in humans; however suvorexant and metabolites has been found to be present in rat milk. Caution should be extended if suvorexant is administered to a nursing woman. |
| **Females and Males of Reproductive Potential** | • No data identified. |
| **BMI and Gender** | • Exposure is increased in obesity defined as >30kg/$m^2$ and in women compared to men. The concentration of suvorexant at 9 hours after dosing (a critical time point for assessing next day morning effects) is predicted to be ~ 20% higher in obese patients than in patients with normal BMI. Obese females have an exposure about 1.5 fold higher than non-obese men. |
| **Respiratory Impairment: COPD/OSA** | • The effects of suvorexant on respiratory function should be considered if prescribed to patients with compromised respiratory function. Suvorexant has not been studied in patients with severe COPD.<br>• COPD: The respiratory depressant effect of suvorexant was evaluated after one night and after 4 consecutive nights of treatment in a randomized, double-blind placebo-controlled, 2 period crossover study in patients (n=25) (aged 18 to 85 years) with mild COPD according to the modified GOLD criteria and a BMI 40kg/m2 or less in patients with mild to moderate obstructive sleep apnea. Suvorexant (40 mg in non-elderly, 30 mg in elderly) did not appear to reduce mean SaO2during total sleep time compared to placebo. Suvorexant was studied in 26 patients with mild to moderate obstructive sleep apnea. Following 40mg suvorexant once-daily for four days, the apnea/hypopnea index treatment difference on day 4 between suvorexant and placebo was 2.7 (90% CI 0.22-5.09). Clinically meaningful respiratory effects of suvorexant in obstructive sleep apnea cannot be excluded. Suvorexant has not been studied in patients with severe obstructive sleep apnea.<br>• OSA: Phase I study: Randomized, placebo-controlled, double-blind, 2-period crossover trial with 26 subjects (aged 18 to 65 years) were evaluated after 4 consecutive nights of suvorexant 40mg. Multiple doses produced a small increase in mean Apena/Hypopnea Index (AHI) by 2.66 (90% CI: 0.22 to 5.09), which is probably clinically insignificant and was not associated with any clinically meaningful decreases in oxygen saturation. The study is limited by it short duration. It is unknown if long term continued use of this product would have more profound effects on respiratory parameters in patients with OSA. |
| **Renal Impairment** | • Suvorexant exposure (expressed as total and unbound concentrations) was similar between patients with severe renal impairment (urinary creatinine clearance ≤ 30 mL/min/1.73$m^2$) and healthy matched control subjects. (data not shown) |
| **Hepatic Impairment** | • No dose adjustment is required in patients with mild or moderate hepatic impairment. However, in an open-label phase I pharmacokinetic trial, 8 adult subjects with moderate hepatic impairment (Child-Pugh score of 7 to 9) and 8 healthy adults received a single dose of suvorexant 20 mg. The half-life was longer in the hepatic impairment subjects at 19.1 compared to healthy subjects at 14.7. Somnolence occurred in 75% (6/8) of the |

| | |
|---|---|
| | hepatic impairment subjects and 63% (5/8) of the control health subjects. Suvorexant is not recommended in patients with severe hepatic impairment (Child-Pugh C) as it has not been studied in this patient population. |
| **Pharmacogenetics/ genomics** | • No data identified |

## Projected Place in Therapy

The National Institutes of Health estimates that roughly 30% of the general population complains of sleep disruption, and approximately 10% have associated symptom of daytime functional impairment. Of interest, in the military service, insomnia has been reported to be as high as 41% in service members deployed to combat and 25% in noncombat areas. Sleep disturbances are common in Veterans with PTSD, TBI, and pain. A recent published study indicates that more than half of the all Veterans (n=917) had clinically significant insomnia symptoms at their initial encounter at VA San Diego Healthcare System between March 2012-August 2013 as measured by the Insomnia Severity Index (ISI). In the subsample without military sexual trauma (n=843), 23.6% had moderate insomnia (ISI 15-21) while 9.6% reported severe insomnia as indicated by the ISI scores of 22-28.

Suvorexant has a different mechanism of action than other approved agents for insomnia. The most common side effect is somnolence. Based on clinical trials, suvorexant offers another option in selected patients whose condition fails to respond or are unable to take other sedative hypnotics such as benzodiazepine and nonbenzodiazepines. Suvorexant long half-life (~12 hours) makes it useful in patients with sleep maintenance insomnia more so than sleep latency. Due to drug-drug interactions, longer exposure in women and obese patients (>30kg/$m^2$) including concern with driving impairment the next day even at the recommended dose, in selected patients, suvorexant may be an alternative to consider.

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## Appendix A: GRADEing the Evidence

Designations of Quality

| Quality of evidence designation | Description |
|---|---|
| High | Evidence includes consistent results from well-designed, well-conducted studies in representative populations that Directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects). |
| Moderate | Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence. |
| Low | Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes. |

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.

# Appendix B:

## Table 1. Phase II: Efficacy and Safety of Suvorexant: Dose Ranging Trial[6]

| Trial/ Purpose | Inclusion/Exclusion/Endpoints | Treatment/Assessment | Results | Adverse Events/Withdrawals |
|---|---|---|---|---|
| Herring et al 2012<br><br>R,DB, PC, MC(29 sites in US plus one in Japan) in a 2-period cross-over PSG study x 4 weeks per treat-ment period | **Inclusion Criteria:**<br>• Between 18 and < 65 years of age in good physical and mental health<br>• Reports total sleep time of ≤ 6.5 hours and a sleep latency of ≥30 minutes on at least 3 out of 7 nights each week within the 4 weeks prior to visit 1, without hypnotic agent<br>• Has ≥1 hour of wakefulness after sleep onset<br>• Spends 6.5 to 9 hours nightly in bed<br>• Regular bedtime hour is between 9 PM and 12 AM<br>• Willing to refrain from napping<br>• Limit alcohol to 2 drinks a day, at least 3 hours before going to bed on non-PSG days, and refrains from drinking alcohol on all PSG visits and at least 24 hours prior to a PSG visit<br>• Willing to limit caffeine consumption to ≤5 standard 6-ounce cups of caffeinated beverages/day<br>• A DSM IV-TR diagnosis of primary insomnia<br>• Not pregnant or willing to use 2 effective forms of contraception for at least 2 weeks prior to and throughout the study<br><br>Screening PSG Inclusion: (Visit 2)<br>• latency to persistent sleep (LPS) > 20 minutes on both PSG nights (first night and 1 week later) and<br>• mean WASO of ≥ 60 minutes on both PSG nights with neither night <45 minutes<br>• Baseline PSG Inclusion (Visit 2)<br>• Patient has LPS > 20 minutes on both screening and baseline PSG nights<br>• Mean WASO ≥60 minutes on the combined Screening and baseline PSG nights<br><br>**Exclusion Criteria:**<br>● clinically significant abnormality (as determined by the investigator) in the following assessments:<br>○ ECG<br>○ SGPT or ALT, SGOT or AST >1.5x upper limit of normal<br>○ Total bilirubin > 1.5 upper limit of normal | Patients receives one of four doses of suvorexant (10, 20, 40, 80 mg) and placebo x 4 weeks with a single-blind placebo washout of a minimum of 7 days between each treatment period.<br><br>**Safety- assessment:**<br>Via adverse event reports, vital signs, EKGs, laboratory parameters, and physical examinations.<br><br>**Residual effects on psychomotor performance**: The Digit Symbol Substitution Test (DSST) and Digit Symbol Copying Test (DSCT) were performed on the morning after PSG nights and within 0.5 to 1 hour after lights on.<br><br>**Withdrawal effects:** Tyrer Withdrawal Symptoms Questionnaire was administered as part of the evening diary on the first 3 days of the 1-week, single blind, placebo washout. Withdrawal effects were considered present if the item at washout days 2 and 3 emerged for the first time or worsened compared with the measurement taken at washout day 1. If the summed item signal was ≥3, the patient was considered to have withdrawal effects.<br><br>**Rebound Insomnia:** evaluated using sTST and sTSO diary measure derived from each of the first 3 nights of the washout period (after period 1). Rebound was defined as a measurement that was worse during the washout-period day than the corresponding mean at baseline. | **Baseline:** Mean age 44.4 ± 11 years; female 58%; Caucasian 70%, mean BMI 26.2 (kg/m$^2$), average Insomnia Severity Index total score was 17, (moderate severity). There was a similar distribution of gender, race, age, and BMI among the treatments.<br>Average Sheehan Disability Scale total score of 9, corresponding to mild disruption of work/social/family life by disease symptoms.<br><br>Table 1: Summary of efficacy of objective PSG of suvorexant vs. placebo on night 1 and 4 weeks and residual effects*<br><br>**Placebo n=249 / Night 1 / End of 4 week**<br>**S10 mg n=62 / S20 mg n=61 / S10 mg n=59 / S20 mg n=57**<br><br>PSG Sleep<br>Primary<br>SE, % (95% CI); p — 65.9 — 5.2 (1.9, 8.6); ≤0.01 (<0.002) — 7.6 (4.2, 11.0); ≤0.001 (<0.002) — 4.7 (1.6,7.8); ≤0.01 (0.003) — 10.4 (7.2, 13.6); ≤0.001 (<0.003)<br>Secondary<br>WASO, min (95% CI); p — 100.7 — -21.2 (-33.5, -8.8); ≤0.001 — -24.7(-37.0,-12.3); ≤0.001 — -21.4 (-34.2, -8.7); ≤0.001 — -28.1(-41.0,-15.1); ≤0.001<br>LPS, min (95% CI); p — 69.3 — -3.4 (-15.6, 8.7) 0.6 — -9.4 (-21.5, 2.9) .13 — -2.3 (-12.2,7.5) 0.6 — -22.3(-32.3,-12.3);† ≤0.001<br>Exploratory<br>TST, min — 316.1 — 25.1 (9.1, 41.2) ≤0.01 — 36.2 (20.1, 52.4) ≤0.001 — 22.3 (7.4, 37.2) ≤0.01 — 49.9(34.7, 65.0) ≤0.001<br>Residual Effects<br>DSST, correct — 59.9 — 0.9 (-2.7, 4.5) — -6.1 (-9.7,-2.4) ≤0.001 — -0.7 (-3.8, 2.3) — -0.7 (-1.7, 4.5)<br>DSCT, correct — 112.6 — 2.8 (-1.0, 6.5) — -0.3 (-4.1, 3.4) — 1.2(-2.5, 4.9) — -0.3 (-4.1, 3.4)<br><br>**Placebo N=249 / Night 1 / End of 4 week**<br>**S40 mg n=59 / S80 mg n=61 / S40 mg n=57 / S80 mg n=55**<br><br>PSG Sleep<br>Primary<br>SE, % (95% CI); p — 65.9 — 10.8 (7.4, 14.2); ≤0.011 (<0.002) — 12.9 (9.5, 16.3); ≤0.001 (<0.002) — 7.8 (4.6, 10.0); ≤0.001 <0.003) — 7.6 (4.4, 10.9); ≤0.001 (<0.003)<br>Secondary<br>WASO, min (95% CI); p — 100.7 — -33.9 (-46.4, -21.5); ≤0.001 — -36.8(-49.4,-24.3); ≤0.001 — -33.2(-46.3, -20.2); ≤0.001 — -28.9 (-42.1,-15.7); ≤0.001<br>LPS, min (95% CI); p — 69.3 — -23.1 (-35.3, -10.9) † ≤0.001 — -25.4 (-37.7, -13.1)† ≤0.001 — -3.8 (-13.8, 6.3)) 0.5 — -9.5 (-19.7, 0.7 0.07<br>Exploratory<br>TST, min — 316.1 — 52.4 (36.2, 68.7) ≤0.001 — 61.9 (45.6., 78.3) ≤0.001 — 36.8 21.6. 52.0)) ≤0.001 — 36.6 (21.1, 52.0) ≤0.001<br>Residual Effects<br>DSST, correct — 59.9 — -2.6 (-6.3, 1.1) — 0.3 (-3.4, 4.0) — -0.6 (-3.8, 2.5) — -0.7 (-1.7, 4.5)<br>DSCT, correct — 112.6 — 0.9 (-4.7, 2.9) — -0.8 (-4.6, 3.0) — -5.1 (-8.9, -1.3) ≤0.01 — -3.5 (-7.3, 0.4)<br><br>SE= total sleep time divided by time in minutes (fixed at 480) x 100 on night 1 and at the end of week 4.<br>DSCT= Digit Symbol Copying Test; DSST= Digit Symbol Substitution Test; LPS= latency to persistent sleep; PSG= polysomnography. †LPS comparison were not significant according to the testing strategy to adjust for multiplicity; however nominal values were ≤0.001 vs. placebo. S=Suvorexant<br>*Sample size yield ~95% power to detect a difference of 8.33 SE, and a correlation of 0.5 between treatment periods. A | 723 Screened/469 excluded/254 randomized/ 228 (90%) completed<br>Discontinuation due to adverse events: 1 suvorexant 80mg (mild visual hallucination);3 placebo<br><br>Table 3: Summary of adverse events of suvorexant 10 and 20 versus placebo<br><br>**P (%) n=249 / S10 (%) n=62 / S20 (%) n=61**<br><br>≥1 AE — 50 (20.1) — 11 (17.1) — 12 (19.7)<br>≥1 drug-related AE — 17 (6.8) — 3 (4.8) — 4 (6.6)<br>≥1 serious AE — 0 — 0 — 0<br>DC due to AE — 3 (1.2) — 0 — 0<br>Common adverse events (≥2 in any group)<br>Somnolence — 1 (0.4) — 1 (1.6) — 3 (4.9)<br>Headache — 6 (2.4) — 0 — 1 (1.6)<br>Dizziness — 0 — 0 — 1 (1.6)<br>Abnormal dreams — 2 (0.8) — 1 (1.6) — 0<br>Sedation — 1 (0.4) — 0 — 0<br>UTI — 2 (0.8) — 0 — 0<br>Upper Respiratory infection — 1 (0.4) — 1 (1.6) — 2 (3.3)<br>Oropharyngeal pain — 2 (0.8) — 0 — 0<br>Muscular weakness — 0 — 0 — 0<br>↑ Alanine aminotransferase — 1 (0.4) — 1 (1.6) — 0<br>↑ CPK — 2 (0.8) — 0 — 0<br><br>AE= Adverse events; S= suvorexant; P=placebo<br>Conclusion:<br>• All doses were more effective than placebo for primary endpoint of SE and for the secondary endpoint of WASO at night 1 and end of week 4.<br>• Post-hoc analysis of LPS using period 1 data to minimize carry-over effect resulted in mean change from baseline for night 1: 10 mg = -19.1, 20mg = -17.4, 40 mg = -31.0, and 80 mg = -22.3; For end of week 4: 10mg = -20.2, 20 mg = -24.6, 40 mg = -15.7, and 80 mg = -19.6. (data not shown)<br>• Potential carryover effect for LPS for patients who received placebo in period 1 had no further improvement in LPS when they received suvorexant in period 2. If patients received suvorexant in period 1, improvement in LPS did not diminish in period 2 even though patients received placebo in period 2. Analyses of the first period |

- Alkaline phosphatase > 1.5 times the upper limit of normal
- Taking any clinically relevant CYP3A4 Inhibitors and inducers; melatonin, antidepressants, BZDs, hypnotics, any CNS depressants, OTCs that could affect sleep, stimulants, antihistamines (sedating), diet pills
- Positive prestudy urine drug screen
- Active Axis I or II disorder as defined in the DSM-IV-TR and assessed by the Mini International Neuropsychiatric Interview.
- Shift work within the past 2 weeks
- >15 cigarettes a day; history (within the last 3 months) of tobacco use associated with initiation or interruption of sleep or requires a cigarette within 30 minutes of waking in the morning
- Narcolepsy; cataplexy, circadian rhythm sleep disorder, sleep-related breathing disorder, restless legs syndrome, parasomnia including nightmare disorder
- HBA1C > 8 %
- BMI >40 kg/m2
- Difficulty sleeping due to a medical condition

Screening PSG Exclusion (Visit 2)

- Apena Hypopnea Index > 10 or
- >10 periodic leg movements associated with an arousal per hour of sleep
- Positive alcohol breath test

Baseline PSG Exclusion (Visit 3)

- Positive alcohol breath test or urine drug screen

**Endpoints:**
Efficacy:
Primary: Sleep efficiency (SE) defined as total sleep time divided by time in minutes (fixed at 480) x 100 on night 1 and at the end of week 4.
Secondary: (trial 1)
WASO (duration of wakefulness after persistent sleep onset to lights on) and LPS (duration of time from lights off to persistent sleep onset) measured on night 1 and at the end of week 4
Exploratory Results:
WASO, LPS (trial 2)
Sleep diary measures: sWASO, sQUAL, SFRESH, sNAW)
Rating scale end points (ISI, CGI-severity, PGI-Severity, PGI-Improvement, PGI-Improvement)

difference of 8.33 in SE corresponds to a 40-minute difference in TST when time in bed is fixed at 8 hours. The study had 93% power to detect a clinically relevant difference on WASO; 64% power to detect a clinically relevant difference on LPS.

Table 2: Summary of efficacy of subjective of suvorexant vs. placebo on night 1 and 4 weeks and residual effects*

| | Placebo n=249 | Night 1 | | End of 4 week | |
|---|---|---|---|---|---|
| | | 10 mg n=62 | 20 mg n=61 | 10 mg n=59 | 20 mg n=57 |
| Subjective Sleep | | | | | |
| Exploratory | | | | | |
| sTST, min | 62.9 | 3.0 (-10.4, 16.4) | -3.1 (-16.8, 10.6) | 5.5 (-6.3, 17.3) | -1.8 ( -13.9, 10.4) |
| sTSO | 342.1 | -2.4 (-8.8, 4.0) | -4.2 (-10.8, 2.3) | -3.0 (-9.3,3.3) | -4.3 (-10.8,2.2) |
| Insomnia Severity Index | | | | | |
| Total Score, (95% CI), p | 16.8 | - | - | -0.4 (-1.7, 1.0) | -2.0 (-3.4, -0.6); ≤0.01 |
| Sheehan Disability Scale | | | | | |
| Total score | 9.30 | - | - | -0.4 (-2.1, 1.3) | -2.0 (-3.8, -0.2) ≤0.05 |
| Work | 3.07 | - | - | -0.3 (-0.0, 0.3) | -0.5 (-1.2, 0.1) |
| Social | 3.23 | - | - | -0.2 (-0.7, 0.4) | -0.7 (-1.3, -0.1) ≤0.05 |
| Family | 3.11 | - | - | -0.1 (-0.7, 0.4) | -0.7 (-1.3,-0.1) ≤0.05 |

| | Placebo n=249 | Night 1 | | End of 4 week | |
|---|---|---|---|---|---|
| | | 40 mg n=62 | 80 mg n=61 | 40 mg n=57 | 80 mg n=55 |
| Subjective Sleep | | | | | |
| Exploratory | | | | | |
| sTST, min | 62.9 | 22.8 (8.6, 36.9) ≤0.01 | 20.8 (6.8, 34.8) ≤0.01 | 29.6 (17.1, 42.1) ≤0.001 | 19.4 (7.1, 31.7) ≤0.01 |
| sTSO | 342.1 | -12.8 (-19.5, 6.0) ≤0.001 | -5.0 (-11.7, 1.7) | -17.4 (-24.1, -10.7) ≤0.001 | -7.7 ( -14.3, -1.1) ≤0.01 |
| Insomnia Severity Index | | | | | |
| Total Score, (95% CI), p | 16.8 | - | - | -1.8 (-3.2, -0.4) ≤0.01 | -1.6 (-3.0, -0.2) ≤0.05 |
| Sheehan Disability Scale | | | | | |
| Total score | 9.30 | - | - | -0.3 (-32.1, 1.5) | 1.1 (-0.7, 2.9) |
| Work | 3.07 | - | - | -0.1 (-0.8, 0.5) | 0.9 (0.3, 1.6) ≤0.01 |
| Social | 3.23 | - | - | -0.2 (-0.8, 0.3) | 0.1 (-0.4, 0.7) |
| Family | 3.11 | - | - | -0.1 (-0.7, 0.5) | 0.2 (-0.4,0.8) |

for only two sequences that included the 10 mg dose revealed no significant effects on either Night 1 or week 4 for the 10 mg dose. The effect of the 10 mg dose on LPS in the first period when pooling all placebo group was as follows:
Night 1: 10mg vs. placebo -21.7 (p=0.011); Month 1: 10 mg vs. placebo -20.6 (p=0.013)

- Increases in TST (exploratory outcome) increased compared to placebo from 22 to 62 minutes depending on the dose and evaluation night. The increase was mainly attributable to greater time spent in REM and stage 2 sleep. When evaluating the percentage of TST spent in each sleep rather than minutes, only REM sleep showed a nominally significant increase vs. placebo for all suvorexant doses.
- Suvorexant 40 and 80 mg doses were superior to placebo for sTSO and sTST
- Suvorexant 10 and 20mg had similar adverse event rate to placebo; although the incidence of somnolence was higher with 20mg compared to 10mg.
- Suvorexant 20, 40 and 80mg showed greater improvement of insomnia compared with placebo as assessed by Insomnia Severity index.
- Median suvorexant AUC is 5 microM/hr which is similar to the lowest AUC which showed effectiveness at all plasma levels. (Data not shown)
- No significant evidence of rebound insomnia upon stopping as evaluated by sTST or sTSO..However, the numbers of patients whose sTST was worse than baseline on any of the first 3 nights of the washout period were 53.4% for placebo; 37.9%, 32.3%, 61.3%, 41.4% for suvorexant 10, 20, 40, and 80mg, respectively.
- No differences were observed regarding withdrawal as assed by the Tyrer Withdrawal Symptom Questionnaire.
- No residual effect as evaluated by DSST and DSCT 9 hours postdose on PSG nights at either night 1 or end of week 4.

Quality Assessment: Fair
Study Critique: Small number of patients; funding provided and study conducted by manufacture of suvorexant
Strength: obvious dose related incidence of adverse events with increasing dose
Weakness: reduced power to adequately determine suvorexant effects on sleep onset;, may not be applicable to VA general population

| | | | | |
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## Appendix C: Acquisition Prices and Cost Considerations

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Prices of Suvorexant as of 6-14-15

| **Drug** | **Dose** | (BIG4) **Price/Day/Patient ($)** | **Price/Year/Patient ($)** |
|---|---|---|---|
| Suvorexant | 5mg | 6.28 | 2,292.20 |
| Suvorexant | 10mg | 6.24 | 2,277.6 |
| Suvorexant | 15mg | 6.24 | 2,277.60 |
| Suvorexant | 20mg | 6.24 | 2,277.60 |

**Note: Prices shown in this internal, draft document may include additional discounts available to VA. This information is considered strictly confidential and must not be shared outside of VA.**