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Abbreviated Class Update: Newer Drugs for Insomnia

Month/Year of Review: November 2014
New drug(s): tasimelteon (Hetlioz™)
suvorexant (Belsomra™)

End date of literature search: August Week 3 2014
Manufacturer: Vanda Pharmaceuticals Inc.
Merck & Co., Inc.

Current Status of Preferred Drug List (PDL) Class:

- Preferred Agents: ZOLPIDEM TABLET
- Non Preferred Agents: ZALEPLON CAPSULE, ZOLPIDEM EXTENDED-RELEASE TABLET, ZOLPIMIST™, LUNESTA™, ROZEREM™, SILENOR™, EDULAR™, INTERMEZZO™

Prior Authorization (PA) Criteria: A quantity limit is in place to prevent chronic daily use of all sedatives (Appendix 2) and to determine if the diagnosis is funded. Treatment of sleep disorders without sleep apnea is not a funded diagnosis (Line 636) by Oregon Health Plan (OHP). Treatment of insomnia contributing to a covered comorbid condition is funded. Electronic step edits were incorporated into the PA process as recommended at the March 2014 P&T meeting to streamline this process. There is also a PA required to prevent a patient from receiving two concurrent oral sedative medications.

Research Questions:

- Is there new comparative effectiveness or safety evidence since the last scan (literature search end date of Week 2, June 2013) of newer drugs for insomnia to warrant a change to the preferred drug list (PDL)?
- Is there evidence that tasimelteon or suvorexant is more effective or safer than currently available newer drugs for insomnia?
- Is there evidence that tasimelteon or suvorexant is more effective of safer for a sub-set of patients with insomnia?

Conclusions:

- There is no new comparative evidence for newer drugs for insomnia since the last scan.
- There is no comparative effectiveness or safety evidence for tasimelteon or suvorexant versus other newer drugs for insomnia.
- There is low level evidence from two small (n= 84, n=20), unpublished, randomized, placebo controlled trials (RCTs) in blind individuals that tasimelteon increases nighttime sleep on the worst 25% of nights by of 50 minutes and decreased daytime sleep on the worst 25% of days by 49 minutes.[1] There is insufficient evidence for adverse drug events of tasimelteon in comparison to placebo.[1]
- There is moderate level evidence from two, unpublished randomized, placebo-controlled trials that suvorexant statistically significantly increases subjective total sleep time by 10-25 minutes and decreases objective waking after sleep onset by 16 -31 minutes.[2] There is low level evidence of no significant adverse drug events for suvorexant in comparison to placebo.[3]

Abbreviated Class Update: Newer Drugs for Insomnia

Recommendations:

- As there is no new comparative evidence for the newer drugs for insomnia it is recommended to compare costs in executive session to determine potential changes to the PDL.
- Compare costs of suvorexant in executive session for PDL placement.
- Make tasimelteon non-preferred in the newer insomnia drug class because there is insufficient evidence for insomnia treatment outside the narrow FDA approved indication and require a prior authorization for a funded OHP diagnosis.

Reason for Review: Tasmelteon was approved by the Food and Drug Administration (FDA) in January 2014 for Non-24-Hour Sleep-Wake Disorder (Non-24).[4] Suvorexant was approved in August 2014 for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.[5]

Previous P&T Conclusions (November 2013):[6,7]

- There is insufficient evidence of superiority or significant clinical advantage of Silenor™ and specialized zolpidem formulations (i.e. Edular™ and Zopimist™) over zolpidem tablets.
- There is good quality evidence that zolpidem and zaleplon are similarly effective for subjective sleep latency.
- There is fair quality evidence that there is no significant difference between zolpidem and eszopiclone on measured sleep outcomes.
- There is insufficient comparative evidence about long-term safety.

Background: The 2014 International Classification of Sleep Disorders classifies sleep disorders into seven categories; insomnia, sleep related breathing disorders, central disorders of hypersomnia, circadian rhythm sleep-wake disorders, parasomnias, sleep related movement disorders, and other sleep disorders.[8] Insomnia is a risk factor for many disorders including coronary heart disease, metabolic syndrome and depression. It is recommended that insomnia patients first get adequate treatment for conditions that may be exacerbating their sleep disturbance.[8,9]

Chronic insomniacs ($\geq$ 3 times per week for > 3 months) have an altered perception of sleep quality where subjective measures, such as self-reported sleep latency (time to fall asleep) or wakefulness after sleep onset (WASO) of more than 30 minutes do not correlate well with similar objective sleep measures derived from polysomnography.[10] The goals of treatment are to reduce the distress and anxiety associated with poor sleep, and to improve daytime function.[10] Behavioral approaches are recommended first-line for chronic insomnia.[8,9] There is moderate level evidence that both benzodiazepine and non-benzodiazepine sedatives moderately reduce the time to sleep onset and increase total sleep time.[9] However, the risks include complex sleep-related behaviors, increased risk of falls and abuse potential[9] Sedatives have not been adequately evaluated for risk versus benefit for long-term use.

The orexin signaling pathway, is a newly identified neurobiological pathway alternative pharmacological target to the γ-aminobutyric acid A receptor system targeted by current sedatives. It originates within the lateral hypothalamus and mediates wakefulness. Antagonism of Orexin-α and orexin-β receptors selectively dampens unwanted wakefulness interfering with sleep.[11,12] Suvorexant is the first orexin receptor antagonist approved.

Circadian rhythm disorders (e.g. Non-24) are characterized by patients falling asleep more than 2 hours later than conventional times.[13] These are thought to be caused by a disruption internal circadian system that is regulated by light signals to the suprachiasmatic nucleus which prevents the pineal gland from producing

melatonin, a hormone that otherwise signals "biological night".[14] Common secondary causes of circadian rhythm disorders include shift work and jet lag. There is no consensus on the appropriate dose or timing of exogenous melatonin for circadian rhythm disorders and it is largely ineffective for shift-work or jet-lag caused insomnia.[13] Ramelteon was the first synthetic melatonin agonist approved but is indicated specifically for sleep onset insomnia and has not been evaluated for circadian rhythm disorders. Tasmelteon is a melatonin agonist at the MT1 and MT2 receptors. It is the only drug FDA approved for Non-24 in blind individuals and was granted orphan drug status.[1] Non-24 is a common complaint of blind patients who cannot receive light signals. Measurement of endogenous melatonin level entrainment is a proposed surrogate outcome for melatonin agonist efficacy for Non-24[15] but this has not been reliably correlated to accepted sleep measures (i.e. sleep latency or WASO).[1] Medical treatment of circadian rhythm sleep disorders also falls below the funding line (i.e. Line 636) on the OHP list of prioritized services.

Methods:
A Medline literature search ending August 2014 for new systematic reviews and randomized controlled trials (RCT's) comparing non-benzodiazepine sedatives for the treatment of insomnia was done. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
None identified.

New Guidelines:
None identified.

Randomized Controlled Trials:
No head to head comparisons were identified.

New Safety Alerts, Indications:

<u>August 2014 - Drug Abuse Warning Network (DAWN)</u>

- "The total estimated number of zolpidem-related emergency department (ED) visits involving overmedication increased for both males and females between 2005-2006 and 2009-2010.
- In 2010, females accounted for two thirds (68 percent) of zolpidem-related ED visits involving overmedication; patients aged 45 to 54 represented the largest proportion of zolpidem-related ED visits involving overmedication.
- More than half of zolpidem-related ED visits involving overmedication in 2010 included other pharmaceuticals combined with zolpidem (57 percent).

- Nearly half (47 percent) of zolpidem-related ED visits involving overmedication resulted in either a hospital admission or transfer in 2010, 26 percent of which were admissions to a critical or intensive care unit."

May 2014 – Ambien™, Ambien CR™ & Edular™

"The U.S. Food and Drug Administration (FDA) is notifying the public that FDA has approved label changes specifying new dosing recommendations for zolpidem products (Ambien, Ambien CR, and Edluar), which are widely prescribed sleep medications. FDA has approved these changes because of the known risk of next-morning impairment with these drugs.

FDA is also warning that patients who take the sleep medication zolpidem extended-release (Ambien CR)—either 6.25 mg or 12.5 mg—should not drive or engage in other activities that require complete mental alertness the day after taking the drug because zolpidem levels can remain high enough the next day to impair these activities. This new recommendation has been added to the Warnings and Precautions section of the physician label and to the patient Medication Guide for zolpidem extended-release (Ambien CR)"

May 2014 - Lunesta™

"The U.S. Food and Drug Administration (FDA) is warning that the insomnia drug Lunesta (eszopiclone) can cause next-day impairment of driving and other activities that require alertness. As a result, we have decreased the recommended starting dose of Lunesta to 1 mg at bedtime. Health care professionals should follow the new dosing recommendations when starting patients on Lunesta. Patients should continue taking their prescribed dose of Lunesta and contact their health care professionals to ask about the most appropriate dose for them."

February 2014 - Lunesta™

"6 ADVERSE REACTIONS
6.2 Post-Marketing Experience..added paragraph

In addition to the adverse reactions observed during clinical trials, dysosmia, an olfactory dysfunction that is characterized by distortion of the sense of smell, has been reported during post-marketing surveillance with LUNESTA. Because this event is reported spontaneously from a population of unknown size, it is not possible to estimate the frequency of this event."

New Drug Evaluation: tasimelteon (Hetlioz™)

FDA approved indications: Non-24-Hour Sleep-Wake Disorder (Non-24).

Potential Off-label Use: Chronic insomnia, other circadian rhythm sleep disorders and depression.

Clinical Efficacy Data: There are 5 completed, placebo-controlled, phase 3 studies (1 for Major Depressive Disorder, 2 for Non-24, 1 for adult primary insomnia, 1 for model of insomnia in health volunteers) and one completed phase 2 study for circadian rhythm disorders in health adult volunteers registered at www.clinicaltrials.gov. No results are posted for any trial. The depression trial (NCT01428661, n=507) was not published, but it was reported that it did not meet its primary endpoint of change in the Hamilton Depression Scale after 8 weeks.[15]

The two trials (NCT01163032 and NCT01430754) submitted to the FDA are published as abstracts only and cannot be evaluated for quality. What follows is a summary of the FDA review.[1] NCT01163032 (FDA ID 3201) was a placebo-controlled, double-blind trial of 84 totally blind patients randomized to tasimelteon 20mg or placebo for 6 months and at a time each day when the patient's circadian rhythm was thought to be coming into alignment based upon urinary melatonin. NCT01430754 (FDA ID 3203) was a randomized withdrawal placebo-controlled study designed to evaluated the long-term maintenance effect of tasimelteon versus placebo. After 11 weeks of treatment, 20 patients were randomized to receive tasimelteon 20mg or placebo. The primary endpoint in both studies was an un-validated surrogate of proportion of patients meeting melatonin entrainment. The FDA did not accept the surrogate and based their determinations on the secondary clinical endpoints of the change from baseline of the nighttime sleep duration on the 25% of nights with the least nighttime sleep and the 25% of days with the most daytime sleep. The baseline was a mean of 195 minutes of nighttime sleep and 137 minutes of daytime sleep. The change was nominally significant for the clinical endpoints of interest in both studies. There was a mean increase of 50 minutes of nighttime sleep on the worst 25% of nights and a mean decrease of 49 minutes of daytime sleep on the worst days.

NCT00490945 and NCT00291187 were published together in Lancet.[16] NCT0049045 was a fair quality, phase II study of 39 healthy volunteers. Subjects were randomized to placebo or tasimelteon 10mg, 20mg, 50mg or 100mg. After 2 weeks of a strict 8 hour sleep schedule they were admitted to a sleep facility where external cues to day and night were eliminated and then a 5-hour phase shift was induced using the study drug 1 hour before bedtime for 3 nights. Tasimelteon 50mg and 100mg increased the primary outcome of mean sleep efficiency by 14.6 – 18.4% over placebo. There was not a statistical difference in WASO, a secondary outcome. NCT00291187 was a good quality, phase III study of 411 healthy volunteers. Patients were maintained on a regular 8-hour sleep schedule for 1 week and then admitted for inpatient study where bedtime was advanced by 5 hours for 1 night. Tasimelteon 50mg and 100mg reduced the primary outcome of mean latency to persistent sleep by 22.6 -26.1 minutes more than placebo and the secondary outcome of WASO by 24.1 – 34 minutes. While these studies both indicate the ability of tasimelton 50mg and 100mg to improve adjustment to an induced, 1 time 5-hour phase shift of sleep in a controlled setting in healthy, young volunteers they are difficult to extrapolate to shift-workers and frequent travelers who may be older, less healthy and need to phase shift more routinely. Of note, only the 20mg dose was approved by the FDA and significant findings were produced by the higher 50mg and 100mg doses.

Clinical Safety: Safety was evaluated by the FDA using a database of 1346 subjects that received at least one dose of tasimelteon, 621 of which got the 20mg dose and 111 were treated 6 months. Only 44 were treated for one year. It was judged adequate for an "orphan indication" and overall there were no safety concerns noted.

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) Sleep Latency as measured by polysomnography
2) Wakefulness after sleep onset as measured by polysomnography

Primary Study Endpoint:

1) Sleep Latency as measured by polysomnography
2) Mean sleep efficiency as measured by polysomnography

Ref./Study Design	Drug Regimens/ Duration	Patient Population	N	Outcomes/ Efficacy Results (CI, p-values)	Safety Results (CI, p-values)	Quality Rating; Internal Validity Risk o Bias/ External Validity Concerns
NCT00490945[16] R-PCT, DB, Phase II 7/14/2004-4/1/2005	-Patients maintained on a regular 8-hour sleep schedule x 2 weeks ther admitted for inpatient study at 2 US sites -single-bed suites free of time cues and had controlled light intensity where induced a 5-hour sleep phase shift x 3 days. Dose of tasimelton varied from 10-100mg	Demographics: 18-50 yrs old mean age: 30's BMI 23-25 Inclusion Criteria: volunteers Exclusion Criteria: -no major sleep disorder - individuals who were adapted to early sleep schedules -good health	ITT: 45 (6 withdrew after the run-in) pbo: 8 t10mg: 9 t20mg: 8 t50mg: 7 t100mg: 7 Attrition: pbo: n=0 (0.00%) t: n=1 (0.03%)	Mean Sleep efficiency Day1 (% of total sleep time asleep as scored by polysomnography): Baseline: 90% pbo: 70.9% p<0.01 vs baseline t10mg: 79.9% t20mg: 82.5% t50mg: 85.5%* t100mg: 89.3%* *p<0.05 vs pbo AD Range: 14.6% - 18.4%) Mean WASO (in minute): Baseline: 34.5 pbo: 106.7 p<0.01 vs baseline t10mg: 79.8 t20mg: 71.9 t50mg: 56.6 t100mg: 41.8	No ADE significantly greater than placebo.	**Quality Rating: Fair** **Internal Validity: RoB** Selection: MOD - unclear process & allocation concealment; stratified by sex Performance: MOD - matched placebo; who was blinded not described Detection: LOW- polysomnography scored by blinded, experienced scorers using standard criteria. Attrition: LOW **External Validity:** Recruitment: volunteers through advertising Patient Characteristics: very young, healthy cohort; probably unrepresentative of shift-workers Setting: model of phase-shift disorder Outcomes: objective polysomnography; a definition of clinically meaningful responders would have been helpful. One night evaluation; unclear if effects would last. **Analysis:** Potentially internally valid, but unclear clinical relevance.

Ref./Study Design	Drug Regimens/ Duration	Patient Population	N	Outcomes/ Efficacy Results (CI, p-values)	Safety Results (CI, p-values)	Quality Rating; Internal Validity Risk o Bias/ External Validity Concerns
NCT00291187[16] R-PCT, DB, Phase III 2/9/2006 – 8/21/2006	Patients maintained on a regular 8-hour sleep schedule x 1 weeks -admitted for inpatient study at 20 US sites, 19 of which did assessments. Bedtime advanced 5 hours x 1 night. Dose of tasimelton varied from 10-100mg	Demographics: 21-50 yrs old Inclusion Criteria: volunteers Exclusion Criteria: -no major sleep disorder - people who had previously slept in a sleep clinic -good health	ITT: 411 pbo:103 t20mg: 100 t50mg: 102 t100mg: 106 Attrition: 0	Mean Latency to Persistent Sleep (in minutes): pbo: 44.6 t20mg: 23.1 t50mg: 18.5* t100mg: 22.0* *p<0.01 vs pbo AD range: 22.6 -26.1 minutes Mean WASO (in minutes) pbo: 140.3 t20mg: 116.2* t50mg: 106.3^ t100mg: 122.3 *p<0.05 vs pbo ^p<0.01 vs pbo AD range: 24.1 – 34 minutes	No ADE significantly greater than pcb	**Quality Rating: Good** **Internal Validity: RoB** Selection: LOW – IVR used Performance: MOD: matched placebo; who was blinded not described Detection: LOW- polysomnography scored by blinded, experienced scorers using standard criteria. Attrition: LOW **External Validity:** Recruitment: volunteers through advertising Patient Characteristics: very young, healthy cohort; probably unrepresentative of shift-workers Setting: model of phase-shift disorder Outcomes: objective polysomnography; a definition of clinically meaningful responders would have been helpful. One night evaluation; unclear if effects would last. **Analysis: I**nternally valid, but unclear clinical relevance.

New Drug Evaluation: suvorexant (Belsomra™)

FDA approved indications: Treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.

Potential Off-label Use: None were identified.

Clinical Efficacy Data: There are 3 completed, placebo-controlled, phase 3 studies, all for insomnia or primary insomnia registered at www.clinicaltrials.gov. Only the long-term safety and tolerability study (NCT01021813) was published and is reviewed below.[3] It and two additional trials (NCT01097616 [n= 1023] and NCT01097629 [n = 1019]) were submitted to the FDA but not published. A phase 2, two-period cross-over study (NCT00792298 [n=254]) was also cited in the FDA review and is published.[11]

NCT01021813 was a fair quality, randomized, blinded, placebo-controlled safety and tolerability study of 781 adult patients with primary insomnia. Patients with primary insomnia were treated with suvorexant 30mg (>65yo) or 40mg (<65yo) or matching placebo tablets every night at bedtime for one year, with a 2 month discontinuation study extension. There was no sample size determination for statistical validity. The primary outcomes were predefined events of clinical interest (i.e. cataplexy, sleep onset paralysis, sleep paralysis, complex sleep related behaviors [e.g. sleepwalking], suicidal ideation or behaviors, falls, hypnogogic or hypnopompic hallucinations, excessive daytime sleepiness, and selected events associated with potential for drug abuse) at one year. There were several threats for alpha error and the secondary efficacy outcomes were patient reported time to sleep onset and total sleep time, both in minutes. The least squares mean change from baseline of subjective time to sleep onset was –26.6 minutes for suvorexant versus -17 minutes for placebo, a difference of –9.7 minutes 95% CI (–16.5 to –2.9), p = 0.0055. The least squares mean change from baseline of subjective total sleep time was –60.5 minutes for suvorexant versus -33 minutes for placebo, a difference of 27.5 minutes 95% CI (16.2 to 38.8), p <0.0001.

The two pivotal efficacy trials are described in the FDA briefing document[2] as parallel group, fixed dose studies in which patients with insomnia were randomized to one of two fixed doses of suvorexant (low dose ages 18-<65-20 mg, >65-15mg; high dose ages 18-<65-40 mg, >65-30mg) or placebo for three months. The primary hypothesis compared the high dose on change from baseline on mean Subjective Total Sleep Time (sTST) and change from baseline on objective WASO at Months 1 and 3. The least squares mean difference in sTST was 19.7 minutes for high dose versus placebo, p <0.00001 and 10.7 minutes for low dose versus placebo p = 0.017 at 3 months for study NCT01097616 and 25.1 minutes for high dose versus placebo p <0.00001 and 22.1 minutes for low dose versus placebo, p=0.00004 at 3 months for NCT01097629. The least squares mean difference WASO was -22.9 minutes for high dose versus placebo, p <0.00001 and -16.6 minutes for low dose versus placebo, p=0.000009 at 3 months for NCT01097616 and -29.4 minutes, p <0.00001 for high dose versus placebo and -31.1 for low dose versus placebo, p=0.000009 at 3 months for NCT01097629. Outcomes at 1 month were similar for the high doses in both studies and somewhat larger for low doses in NCT01097616. The clinical significance of the differences is debatable but are nominally similar to the effect size seen with the benzodiazepine and non-benzodiazepine sedatives currently on the market.

NCT00792298[11] was a good quality, randomized, placebo-controlled, 2-period, cross-over trial which consisted of patients who received one of 4 doses of suvorexant (10, 20, 40, or 80 mg) and placebo. Each treatment period was 4 weeks, with a single-blind placebo washout period of at least one week between periods. Patients were assessed with a polysomnography on nights 1 and 28 of each period. The primary outcome was Sleep Efficiency, defined as 100 multiplied by Total Sleep Time (in minutes) divided by Time in Bed (in minutes). The Time in Bed was fixed at 8 hours. Suvorexant showed statistically significant dose-

related improvements versus placebo on the co-primary end points of sleep efficiency at night 1 and night 28 though it is difficult to interpret the clinical relevance of this outcome. Dose-related effects were also observed for secondary outcomes including WASO which declined by 21 – 37 minutes.

Clinical Safety: NCT01021813[3] provided information on safety and tolerability of suvorexant at 1 year. The small sample size, very low event rates and relatively healthy patient population prohibit confident conclusions regarding safety as no outcome reached statistical significance. NCT00792298[11] did not identify any adverse drug events. The FDA briefing document[2] states that "… a total of 2027 patients with insomnia have received at least one dose of suvorexant; 1218 for at least 3 months, 507 for at least 6 months, and 160 for at least one year." It also reports that only somnolence occurred at a significantly higher rate than placebo (e.g. at 3 months placebo 3% vs low dose suvorexant 7% and high dose suvorexant 11%).

The Drug Enforcement Agency placed suvorexant in Schedule IV.[17]

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) Sleep Latency as measured by polysomnography
2) Wakefulness after sleep onset as measured by polysomnography
3) Withdrawals due to adverse events

Study Endpoint:

1) Sleep Efficiency defined as total sleep time as measured by polysomnography divided by time in bed in minutes
2) Subjective time to sleep onset (sTSO, min), least squares mean change from baseline
3) Subjective total sleep time (sTST, min), least squares mean change from baseline
4) Pre-specified events of clinical interest: cataplexy, sleep onset paralysis, sleep paralysis, complex sleep related behaviors (e. g. sleepwalking), suicidal ideation or behaviors, falls, hypnogogic or hypnopompic hallucinations, excessive daytime sleepiness, and selected events associated with potential for drug abuse.

Ref./Study Design	Drug Regimens / Duration	Patient Population	N	Outcomes/ Efficacy Results	Safety Results (listed in descending order of event rate)	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
NCT01021813[3] R-PCT, DB, Phase III 12/2009 - 8/2011 106 sites in Americas, Australia, Europe, & South Africa The primary objective was to assess the safety and tolerability of suvorexant for up to 1 year.	Intervention: S: 30mg (≥65yo) or 40mg (<65yo) qHS P: matching tablets qHS @ 1 year, S patients randomly assigned in a 1:1 ratio a continuation of their previous dose or to switch to placebo x 2 additional months. P patients remained on placebo. Follow-up: - Patients seen @ week 2 & months 1, 3, 6, 9, 12, 13, 14 with phone calls at each of the intervening months. - Safety assessment self-reported, open-ended questions. - Columbia Suicide Severity Rating Scale, laboratory & ECG @ clinic visits. - Motor Vehicle Accidents and Violations - questionnaire administered at scheduled clinic visits or phone calls - The Quick Inventory of Depressive Symptomatology—Self Report - (QIDS-SR)18 was administered at clinic visits starting at month 1 to assess mood. - Tyrer Withdrawal Symptom Questionnaire was administered before dosing for three consecutive evenings at the start of the randomised discontinuation phase.	Demographics: Age: 61.5 yo (mean) BMI: 27% (overweight) White: 90.5% N.Amer. 61.5% Disease severity measures similar at baseline. Inclusion Criteria: ->18 yo; - primary insomnia assessed by a clinical interview and a structured sleep diagnostic interview Exclusion Criteria: - potentially confounding neurological disorders, major affective or psychotic illness, substance abuse, or an unstable medical disorder.	ITT: S: 522 SS:156 SP:166 P: 259 mITT*: S: 517 SS:152 SP:160 P: 254 *excluded 1 patient in each group who did not take the drug and 4 in each group missing baseline information. Attrition: S: 14/522 (2.7%) P: 12/259 (4.6%) Non-Adherence: S: 200/522 (38.3%) P: 97/259 (37.5%) (reasons similar between groups) Statistical Analysis: -The planned S:500 and P:250 with not >60% in either non-elderly or elderly age groups. -Sample size driven by regulatory guidelines to study at least 100 suvorexant-treated patients in each age group for at least 1 year rather than formal statistical considerations.	Per Protocol Analysis Used: S: 298 P: 147 Subjective total sleep time, least squares mean change from baseline in minutes @ 1 year: S: 60.5 (54.0 to 66.9) P: 33.0 (23.7 to 42.2) Diff: 27.5 (16.2 to 38.8) p <0.0001 Subjective time to sleep onset least squares mean change from baseline in minutes @ 1 year: S: –26.6 (–30.5 to –22.7) P: –17.0 (–22.6 to –11.4) Diff: –9.7 (–16.5 to –2.9) p = 0.0055	Withdrawals d/t ADE: S: 61/522 (11.7%) P: 22/259 (8.5%) RR: 1.38 95% CI (0.86, 2.19) ARI: 3.2% Events associated with potential for drug abuse: S: 18 (3.5%) - P: 10 (3.9%) ARR: 0.4% 95% CI (-3.8%,2.2%) Falls: S: 12 (2.3%) - P: 8 (3.1%) ARR: 0.8% 95% CI (-3.9%,1.5%) Excessive daytime sleepiness: S: 13 (2.5%) - P: 2 (0.8%) ARI: 1.7% 95% CI (-0.5%,3.6%) Suicidal ideation: S: 4 (0.8%) - P: 0 ARI: 0.8% 95% CI (-0.7%,2.0%) Hypnogogic hallucinations: S: 3 (0.6%) - P: 0 ARI: 0.6% 95% CI (-0.9%,1.7%) Sleep onset paralysis: S: 1 (0.2%) - P: 0 ARI: 0.2% 95% CI (-1.3%,1.1%) Sleep paralysis: S: 2 (0.4%) - P: 0 ARI: 0.4% 95% CI (-1.1%,1.4%) Complex sleep-related behaiors: S: 1 (0.2%) - P: 0 ARI: 0.2% 95% CI (-1.3%,1.1%) Hypnopompic hallucinations: S: 1 (0.2%) - P: 0 ARI: 0.2% 95% CI (-1.3%,1.1%) Cataplexy: S: 0 - P: 0	**Quality Rating: FAIR** **Internal Validity: RoB** Selection: LOW - IVR system allocated a computer generated randomisation schedule (2:1, suvorexant:placebo) based on input from a masked Merck statistician. Stratified by age (non-elderly vs elderly) & region. Performance: LOW - Treatment allocation was masked from study investigators, site staff, patients, and Merck monitoring staff throughout the study. Suvorexant or placebo were provided as matching tablets. Detection: LOW - Treatment allocation was masked from study investigators, site staff, patients, and Merck monitoring staff throughout the study. Suvorexant or placebo were provided as matching tablets. An adjudication committee of three non-Merck experts in neurology, psychiatry, and sleep adjudicated prespecified events of clinical interest including events potentially suggestive of intrusion of rapid eye movement (REM),sleep into wakefulness (cataplexy) or initiation of sleep (sleep onset paralysis). Attrition: HIGH – almost 40% non-adherence to protocol/withdrawals. Reasons for withdrawal between groups similar but difficult to assess if randomization was maintained. 5 patients from each group excluded from analysis (i.e. mITT). Sample size was not calculated and multiple outcomes were assessed. **External Validity:** Recruitment: patients identified by investigators; a 1-week single-blind placebo run-in screening phase (295/1076 [27%] failed the screen. High risk of selecting patients more likely to respond favorably. Patient Characteristics: Older, white, healthy population uncharacteristic of general population requesting sleep medications. Setting: academic & private investigational centers may be unrepresentative of ambulatory care population in US. Outcomes: Subjective efficacy outcomes used and efficacy was secondary. Multiple outcomes assessed with high likelihood of multiplicity alpha error given no sample size determination. **Analysis:** Subjective efficacy outcomes of <30minutes difference in total sleep time and <10minutes difference in time to sleep are of questionable clinical relevance. They reach statistical thresholds but there are multiple threats (low sample size, multiple outcomes, secondary outcomes) for alpha error.

Ref./Study Design	Drug Regimens / Duration	Patient Population	N	Outcomes/ Efficacy Results	Safety Results	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
NCT00792298[11] R-PCT, DB, Phase III 11/2008 – 12/2009 29 sites in US & 12 sites in Japan 2-period crossover polysomnography study to assess 4 doses of suvorexant (10, 20, 40, 80 mg) in patients with primary insomnia.	Intervention: 10mg/P P/10mg 20mg/P P/20mg 40mg/P P/40mg 80mg/P P/80mg Patients received the first named treatment in period 1 (up to 4 weeks) and the second named treatment in period 2 (up to 4 weeks), with a 1-week washout between treatment periods.	Inclusion: -18 to 64 years old -good physical & mental health -diagnosed with primary insomnia based on DSM-IV-TR criteria. - confirmed polysomnography of latency to persistent sleep (LPS) of >20 minutes on both night 1 & 7 of run-in period mean WASO of ≥60 minutes on both nights with neither night <45 minutes Exclusion: -reported in supplementary material only Demographics - mean age 44 yo ~BMI 26 ~85-86% US ~70% white Insomnia Severity Score ~17 measured parameters fairly similar at baseline.	ITT: 10mg/P: 31 P/10mg: 32 20mg/P: 33 P/20mg: 32 40mg/P: 32 P/40mg: 32 80mg/P: 31 P/80mg: 31 Total: 254 Attrition: 80mg/P: 1/31 (3.2%) Total: 1/254 (0.4%) Non-Adherence: 10mg/P: 2/31 (6.5%) P/10mg: 2/32 (6.3%) 20mg/P: 3/33 (9.1%) P/20mg: 6/32 (18.8%) 40mg/P: 2/32 (6.3%) P/40mg: 5/32 (15.6%) 80mg/P: 3/31 (9.7%) P/80mg: 3/31 (9.7%) Total: 26/254 (10.2%) Sample Size: The study was planned to enroll approximately 250 randomized patients to yield approximately 208 patients total completing both periods of the crossover study. In order to protect the experiment-wise Type I error of 5%, the highest dose was compared to placebo, and needed to be significant (p=0.05) at both time points (Night 1 and Week 4) in order to test the next highest dose in the same way.	PRIMARY OUTCOMES: Least Squares Mean Change from placebo Sleep Efficiency* Night 1: 10 mg: 5.2 p<0.01 20 mg: 7.6 p<0.001 40 mg: 10.8 p<0.001 80 mg: 12.9 p<0.001 Least Squares Mean Change from placebo Sleep Efficiency* Night 28: 10 mg: 4.7 p<0.01 20 mg: 10.4 p<0.001 40 mg: 7.8 p<0.001 80 mg: 7.6 p<0.001 SECONDARY OUTCOMES: Difference in least squared neans at Night 1 WASO in minutes: 10 mg: -21.2 p<0.001 20 mg: -24.7 p<0.001 40 mg: -33.9 p<0.001 80 mg: -36.8 p<0.001 Difference in least squared neans at Night 28 WASO in minutes: 10 mg: -21.4 p=0.001 20 mg: -28.1 p<0.001 40 mg: -33.2 p<0.001 80 mg: -28.9 p<0.001	Withdrawal d/t ADE: P: 3 (12%) 80mg: 1 (1.6%) No serious ADEs reported. No ADE significantly higher than placebo except somnolence.	**Quality Rating: GOOD** **Internal Validity: RoB** Selection: LOW - assigned to treatment using a computer-generated randomized allocation schedule prepared by Merck and implemented through an interactive voice response system. Randomization was stratified according to country (United States, Japan). Performance: LOW - A double-dummy design was used to maintain blinding. Study investigators, site staff, patients, PSG scorers, and Merck monitoring staff remained blinded to treatment allocation throughout the study. Detection: LOW - Visual scoring of polysomnography data was performed by blinded personnel at Henry Ford Hospital Sleep Disorders and Research Center (Detroit, MI), in 30-second epochs according to the scoring standards developed by the American Academy of Sleep Medicine. Attrition: MOD- sample size was met; per protocol analysis was done excluding ~2% of patients. There was ~10% overall non-adherence to the protocol through-out the short study period increasing chance of dissimilar groups. Multiplicity accounted for with hierarchical testing. Overall small sample with multiple outcomes increases chance for alpha error. **External Validity:** Recruitment: patients identified by investigators; a 1-week single-blind placebo run-in. 469/723 (65%) excluded on screening. High risk of selecting patients more likely to respond favorably. Patient Characteristics: younger, white, healthy population uncharacteristic of general population requesting sleep medications. Setting: Not reported other than ~70 US/30% Japan. Outcomes: Objective outcomes confirmed with polysomnography. Primary outcome difficult to interpret clinically. Secondary WASC outcome effect size similar to other sedatives. Unfortunately, short study duration limits ability to extrapolate results to longer duration. **Analysis:** Probably internally valid but difficult to extrapolate.

* Defined as total sleep time as measured by polysomnography divided by time in bed in minutes [fixed at 480 for this study] multiplied by 100 on night 1 and at the end of week 4.

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Appendix 1: Specific Drug Information Tasimelteon (Hetlioz™) [4]

CLINICAL PHARMACOLOGY

Tasimelteon is a melatonin MT1 and MT2 receptor agonist. These receptors are thought to regulate circadian rhythms.

PHARMACOKINETICS[1]

Parameter	Result
Oral Bioavailability	NR
Protein Binding	90%
Elimination	80% recovered via metabolites in urine 4% recovered via metabolites in feces
Half-Life	1.3 hours
Metabolism	Extensively metabolized. CYP1A2 and CYP3A4 are the primary isoenzymes involved

DOSE & AVAILABILITY[1]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	Pregnancy Category	OTHER DOSING CONSIDERATIONS
20mg	Oral	Before bedtime	Tablet		Not studied in patients with severe hepatic impairment (Child-Pugh Class C)	Not established	2x increase in levels	C	-Take without food; -Drug effect may not occur for weeks or months -Smokers metabolize it quicker.

DRUG SAFETY[1]

Serious (REMS, Black Box Warnings, Contraindications): None

Warnings and Precautions: None

Look-alike / Sound-alike (LA/SA) Error Risk Potential: Halcion, Haldol, Healon, tramadol, trazadone

Appendix: Specific Drug Information - suvorexant (Belsomra™)[5]

CLINICAL PHARMACOLOGY

"The mechanism by which suvorexant exerts its therapeutic effect in insomnia is presumed to be through antagonism of orexin receptors. The orexin neuropeptide signaling system is a central promoter of wakefulness. Blocking the binding of wake-promoting neuropeptides orexin A and orexin B to receptors OX1R and OX2R is thought to suppress wake drive."[5]

PHARMACOKINETICS[5]

Parameter	Result
Oral Bioavailability	82% (mean of 10mg)
Protein Binding	>99%
Elimination	23% recovered via metabolites in urine 66% recovered via metabolites in feces
Half-Life	12 hours
Metabolism	Primarily metabolized: primarily by CYP3A with a minor contribution from CYP2C19.

DOSE & AVAILABILITY[5]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	Pregnancy Category	OTHER DOSING CONSIDERATIONS
5 mg 10 mg 15 mg 20 mg	Oral	Before bedtime	Tablet	No dose adjust-ment is required	Not rec. for patients with severe hepatic impairment	Not established	No clinically meaningful differences were observed	C	-Use the lowest effective dose. -Recommended dose is 10 mg, within 30 minutes of going to bed, with at least 7 hours remaining before the planned time of awakening. Do not to exceed 20 mg once daily. -Time to effect may be delayed if taken with or soon after a meal.

DRUG SAFETY[5]

Serious (REMS, Black Box Warnings, Contraindications): No REMS or Black Box warnings. Do not use in patients with narcolepsy.

*Warnings and Precautions: "*Daytime somnolence: Risk of impaired alertness and motor coordination, including impaired driving; risk increases with dose; caution patients taking 20 mg against next-day driving and other activities requiring complete mental alertness. Need to evaluate for co-morbid diagnoses: Reevaluate if insomnia persists after 7 to 10 days of treatment."

Look-alike / Sound-alike (LA/SA) Error Risk Potential: belladonna

Appendix 3: Current PA Criteria

Central Nervous System (CNS) Sedatives –Quantity Limit

Goal(s):

- Approve only for covered OHP diagnoses.
- Treatment of uncomplicated insomnia is not covered, but insomnia contributing to covered comorbid conditions is.
- Prevent adverse events associated with long-term sedative use.
- Clients coming onto the plan on chronic sedative therapy are grandfathered.(refer to criteria). Also see related Sedative Therapy Duplication edit. The safety and effectiveness of chronic sedative use is not established in the medical literature.

Length of Authorization:

- 6 to 12 months (criteria specific)

Requires PA:

- All CNS sedatives in Standard Therapeutic Class 47 that exceed 15 doses per 30 days.

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org
- Trazodone, mirtazapine, diphenhydramine or tricyclic antidepressants may be alternatives for some clients.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Does client have diagnosis of insomnia with sleep apnea, ICD9: 780.51?	Yes: Go to #3.	No: Go to #4.
3. Is client on CPAP?	Yes: Approve for up to 1 year. The use of CPAP essentially negates the sedative contraindication and they are often prescribed to help clients cope with the mask.	No: Pass to RPH, Deny, (Medical appropriateness). Due to the depressant effects of sedative/ hypnotics, sedative/hypnotics are contraindicated for this diagnosis and are not approvable.

Approval Criteria		
4. Is the client being treated for co-morbid depression,/ bipolar disorder (296.xx) OR anxiety / panic disorder (300.0x) AND Is there an existing claim history of antidepressants, lithium, antipsychotics, or other appropriate mental health drugs?	Yes: Approve for up to 1 year.	No: Pass to RPH; Go to #5.
5. RPH only: Is diagnosis being treated a covered indication on the OHP and is there medical evidence of benefit of the prescribed sedative? All indications need to be evaluated as to whether they are above the line or below the line.	Above: Document supporting literature and approve up to 6 months with subsequent approvals dependent on f/u and documented response.	Below: Go to #6.
6. RPH only: Is this a request for continuation therapy for client with history of chronic use where discontinuation would be difficult or unadvisable? NOTE: Clients coming onto the plan on chronic sedative therapy are "grandfathered."	Yes: Document length of treatment and last follow-up date. Approve for up to 1 year.	No: Deny, (Medical Appropriateness)

P&T / DUR Action: *11/20/14, 3/27/14, 11/21/13, 5/18/06, 2/23/06, 11/10/05, 9/15/05, 2/24/04, 2/5/02, 9/7/01*
Revision(s): *??/??/14; 1/1/07, 7/1/06, 11/15/05*
Initiated: *11/15/02*