PDL NEW DRUG REVIEW

Proprietary Name: Belsomra®
Common Name: suvorexant
PDL Category: Sedative/Hypnotics- Non-Benzodiazepines

Comparable Products	Preferred Drug List Status
Zaleplon	Preferred
Zolpidem	Preferred
Zolpidem ER	Non-Preferred with Conditions

Summary

Indications and Usage: For the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance. This is a pregnancy category C medication. The safety and efficacy of use in children have not been established.

Dosage Forms: Film-Coated Tablets: 5mg, 10mg, 15mg, and 20mg

Recommended Dosage: The lowest effective dose should be used. Take 10mg once per night within 30 minutes of going to bed and with ≥7 hours remaining before the planned time of awakening. If the 10mg dose is tolerated but not effective, the dose may be increased to a maximum of 20mg. Dose adjustments are not required in those with renal or mild-to-moderate hepatic impairment. Belsomra® has not been studied in those with severe hepatic impairment, thus use in this population is not recommended.

Belsomra® exposure is increased in obese vs non-obese patients and in women vs men. Therefore, the increased risk of exposure-related adverse effects should be considered prior to increasing the dose, especially in obese women.

Due to the potential for additive effects, Belsomra® dose adjustments may be needed if it is used concomitantly with other CNS depressants. In addition, concomitant use with alcohol should be avoided. The Belsomra® dose should be adjusted to 5mg daily if used concomitantly with moderate CYP3A inhibitors, up to a 10mg daily dose maximum. The concomitant use of Belsomra® with strong CYP3A inhibitors is not recommended.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Belsomra®20mg in non-elderly or 15mg in elderly patients) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same for both drugs of that the incidence for the active drug was less than placebo.* Reported adverse events included diarrhea (1%), dry mouth (1%), upper respiratory tract infection (1%), headache (1%), somnolence (4%), dizziness (1%), abnormal dreams (1%), and cough (1%).

Belsomra® may cause CNS depressant effects and can impair daytime wakefulness even when used as prescribed. Somnolence and other CNS depressed effects should be monitored. In addition, driving skills can be impaired with use and may increase the risk of falling asleep while driving. Those taking the 20mg dose should be cautioned against next-day driving and other activities that may require full mental alertness; however, those taking lower doses should also be cautioned about this potential of driving impairment.

A dose-dependent increase in suicidal ideation was seen in clinical trials with patients taking Belsomra®. It is recommended to seek immediate evaluation if new behavioral signs or symptoms appear. In addition, cognitive and behavioral changes have been reported with hypnotics, such as Belsomra®. Reports of 'sleep-driving' and other complex behaviors have been associated with hypnotic use. It is recommended to discontinue Belsomra® if these behaviors are reported.

Use has not been studied in those with severe obstructive sleep apnea (OSA) or severe chronic obstructive pulmonary disease (COPD).

Contraindications: In patients with narcolepsy

Manufacturer: Merck

Analysis: Suvorexant, the active ingredient of Belsomra®, is a highly selective antagonist for orexin receptors OX1R and OX2R. The orexin neuropeptide signaling system is a central promoter of wakefulness; therefore, by blocking the binding of wake-promoting neuropeptides orexin A and orexin B to receptors OX1R and OX2R it is thought to subdue the wake drive. Nevertheless, antagonism of the orexin receptors may also cause potential adverse effects, such as signs of narcolepsy/cataplexy.

Three studies were performed to assess the safety and efficacy of Belsomra® when used in patients with insomnia characterized by difficulties with sleep onset and sleep maintenance. Study 1 and Study 2 (N=740 total) were similarly designed multicenter, randomized, double-blind, placebo-controlled studies that included non-elderly (age 18-64) and elderly (≥65 years) who were randomized separately. Non-elderly were randomized to 20mg Belsomra® (or placebo) while elderly patients were randomized to 15mg Belsomra® (or placebo).

Results of Study 1 and Study 2 suggested that Belsomra® was superior to placebo for sleep latency per polysomnography (objectively) and by patient-estimated sleep latency (subjectively). In addition, it was superior to placebo for sleep maintenance per polysomnography (PSM) and patient-estimated total sleep time. These results are illustrated in the table below, which was adapted from the prescribing information.

	Change from baseline after 1 & 3 months (Minutes)		Difference between Belsomra® & placebo (Minutes)
Polysomnographic assessment of time to sleep onset (minutes)			
	Placebo	Belsomra®	
Month 1	-23 (Study 1) -25 (Study 2)	-34 (Study 1) -33 (Study 2)	-10 (p<0.001) -8 (p<0.05)
Month 3	-27 (Study 1) -29 (Study 2)	-35 (Study 1) -29 (Study 2)	-8 (p<0.01) 0
Patient-estimated time to sleep onset (minutes)			
Month 1	-12 (Study 1) -14 (Study 2)	-17 (Study 1) -21 (Study 2)	-5 -7 (p<0.05)
Month 3	-17 (Study 1) -21 (Study 2)	-23 (Study 1) -28 (Study 2)	-5 (p<0.05) -8 (p<0.05)
Polysomnographic assessment of sleep maintenance (wake after sleep onset; minutes)			
Month 1	-19 (Study 1) -23 (Study 2)	-45 (Study 1) -47 (Study 2)	-26 (p<0.001) -24 (p<0.001)
Month 3	-25 (Study 1) -25 (Study 2)	-42 (Study 1) -56 (Study 2)	-17 (p<0.001) -31 (p<0.001)
Patient-estimated total sleep time (minutes)			
Month 1	23 (Study 1) 22 (Study 2)	39 (Study 1) 42 (Study 2)	16 (p<0.001) 21 (p<0.001)

	Change from baseline after 1 & 3 months (Minutes)		Difference between Belsomra® & placebo (Minutes)
Month 3	41 (Study 1) 38 (Study 2)	51 (Study 1) 60 (Study 2)	11 ($p<0.05$) 22 ($p<0.001$)

Study 3 was a 1-month, crossover study that included non-elderly adults who were treated with either placebo (N=249) or Belsomra® 10mg (N=62), 20mg (N=61), or up to 80mg. Results suggested that Belsomra® was superior to placebo for sleep latency and sleep maintenance as assessed by polysomnography. While higher doses of Belsomra® were also assessed in Study 1 and Study 2, results found that higher doses had similar efficacy to the lower doses but had significantly more adverse reactions.

Several safety studies have been performed, including assessing the effects of Belsomra® on driving. Results suggested clinically meaningful impaired driving performance in some subjects. Therefore, the warnings of next-day driving and other activities needing full-mental alertness as discussed above were developed. A 3 month controlled study assessed the effect of rebound insomnia in non-elderly adults after discontinuation of Belsomra®. Results suggested that there were no clear effects on sleep onset or maintenance seen. In a withdrawal study, there was no clear evidence of withdrawal following discontinuation of Belsomra® in the overall study population.

Place in Therapy: At least one noted reference source recommends that cognitive behavioral therapy (CBT) be used as initial therapy for those who have insomnia that is severe enough to need an intervention. If CBT is not enough, it is suggested to add a medication, with a short-acting medication recommended for sleep onset insomnia and a long-acting medication recommended for sleep maintenance insomnia. As Belsomra® is new and there are no comparator studies with other therapies, the authors note that its role for treatment of insomnia has yet to be established.

There is no evidence at this time to support that Belsomra® is safer or more effective than the currently available, more cost effective medications, based on data reviewed from registration trials in the package insert as well as a review of current recommendations on the treatment of insomnia. It is therefore recommended that Belsomra® remain non-preferred and require prior authorization and be available to the few who are unable to tolerate or who have failed on preferred medications.

PDL Placement:

- ☐ **Preferred**
- ☒ **Non-Preferred with Conditions**
- ☐ **Preferred with Conditions**

References

[1] Belsomra [package insert]. Whitehouse Station, NJ: Merck & Co; 2014.

[2] UpToDate. Treatment of insomnia. Desktop version. Accessed January 2015.