

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204569Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategy (REMS) Memo**

Date: June 28, 2013

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Drug Name(s): suvorexant

Therapeutic Class: Orexin receptor antagonist (first in class)

Dosage and Route: 5 mg, 10 mg, 15 mg and 20 mg oral (immediate-release) tablets

Indication(s): Insomnia

Application Type/Number: NDA 204-569

Applicant/sponsor: Merck Sharp & Dohme Corp. (Merck)

OSE RCM #: 2012-2818

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## 1 INTRODUCTION

An application for suvorexant NDA 204-569 was submitted to the Division of Neurology Products (DNP) by Merck Sharp & Dohme Corp. on August 29, 2012. Even though the Applicant did not propose a risk evaluation and mitigation strategy (REMS), the Division of Risk Management (DRISK) was consulted by DNP for participation in the approval process because the proposed drug is a new molecular entity (NME). This memorandum evaluates if a REMS is needed for suvorexant.

Suvorexant is the first reversible orexin receptor antagonists in clinical development for the treatment of insomnia. The proposed indication is for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance in adult patients. The dosing instructions are as follows:

- Use the lowest effective dose for the patient
- Recommended dose 10 mg, no more than once per night, taken 30 minutes before bedtime, with at least 7 to 8 hours remaining before the planned time of awakening
- Dose may be increased if lower doses are not effective (up to 20 mg once daily)
- Recommended dose 5 mg when used with moderate CYP3A4 inhibitors (dose may be increased up to 10 mg once daily if the 5 mg dose not effective)

### 1.1 MATERIALS REVIEWED

- Mid-Cycle Meeting Clinical Review-slides (K. Illoh)
- Peripheral and Central Nervous System Drugs Advisory Committee (PCNS) Meeting-meeting notes (dated May 23, 2013)

### 1.2 OVERVIEW OF CLINICAL PROGRAM

Suvorexant facilitates the sleep process by reversibly blocking the binding of “wake-promoting” neurotransmitters (orexin A and orexin B) to orexin receptors (OX1R and OX2R). Inhibition of orexin A and B binding promotes the brain’s transition from a state of wake to sleep. The drug has no pharmacological affinity for receptors that bind to gamma-aminobutyric acid (GABA), dopamine, serotonin, noradrenaline, melatonin, histamine, acetylcholine or opiates. Suvorexant is extensively bound to human plasma proteins and primarily eliminated by CYP3A metabolism with a minor contribution from CYP2C19.<sup>1,2</sup>

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<sup>1</sup> Merck Sharp & Dohme Corp. Original New Drug Application Submission No.204-569 for MK-4305 (Suvorexant) dated August 29, 2012.

<sup>2</sup> Merck Sharp & Dohme Corp. Suvorexant Original Marketing Application dated August 9, 2012.

The clinical program for suvorexant was designed to demonstrate that the drug improves conditions of sleep onset and sleep maintenance, is effective for acute and chronic use, and is generally safe and well-tolerated.

### **Safety and Efficacy Trials**

The safety and efficacy of suvorexant for use in elderly and non-elderly patients with chronic insomnia was primarily assessed through three placebo-controlled Phase 3 trials:

1. 3-month efficacy and safety trial using high dose (HD) suvorexant [40 mg in non-elderly patients (<65 yrs) and 30 mg in elderly patients] and low dose (LD) suvorexant [20 mg in non-elderly patients (<65 yrs) and 15 mg in elderly patients]

Note: A 3-month “optional” extension was available to patients in this trial, following the 3-month core treatment phase to collect additional long-term safety data on HD and LD suvorexant for up to 6 months of treatment

2. 3-month efficacy and safety trial using high dose (HD) suvorexant [40 mg in non-elderly patients (<65 yrs) and 30 mg in elderly patients] and low dose (LD) suvorexant [20 mg in non-elderly patients (<65 yrs) and 15 mg in elderly patients]
3. 12-month safety trial for both elderly and non-elderly patients using HD suvorexant

Note: This study also included a 2-month “Randomized Discontinuation Phase” in which additional safety and supportive efficacy data was collected beyond the 12 months (up to 14 months)

Additional safety studies included a 4-week, placebo-controlled, dose-finding Phase 2 study in non-elderly adults and the following Phase 1 trials:

- Two Driving studies
- One study to assess nighttime safety and psychomotor performance
- Three studies to assess respiratory function [1 in patients with mild to moderate Chronic Obstructive Pulmonary Disease (COPD), 1 in patients with mild to moderate Obstructive Sleep Apnea (OSA) and 1 in normal adults]

### *Safety*

The most common adverse reactions (reported in 5% or more of patients treated with suvorexant reported in the Phase 3 confirmatory efficacy trials were somnolence (10.7% and 6.7% in high (40 mg and 30 mg) and low dose (20 mg and 15 mg) in non-elderly and elderly patients versus 3% in placebo patients) and headache (7.3% and 6.6% in high (40 mg and 30 mg) and low dose (20 mg and 15 mg) versus 6.0% in placebo patients). In the long term safety trial, 13.2% of suvorexant patients experienced somnolence versus 2.7% of placebo patients. In the Phase 3 patients, over 0 – 12 months, serious adverse events occurred in 2.8% of high dose suvorexant patients and 3.2% of patients on placebo.

In the overall population of patients with insomnia treated with the recommended doses of suvorexant, no clinically meaningful next day impairment of psychomotor

performance was observed compared to placebo. There was no significant impairment of next-day driving performance after one night and 8 consecutive nights of suvorexant dosed at 15 or 30 mg in elderly, 20 or 40 mg in non-elderly subjects. However, some subjects had changes suggestive of impaired driving performance following treatment with suvorexant. Due to individual variation, patients should be advised not to drive, operate machinery or engage in other activities requiring full mental alertness until they feel fully awake.

Three studies showed no significant effects on memory or balance compared to placebo. In a fourth study in healthy non-elderly subjects, there was a significant decrease in word recall after the words were presented to subjects in the morning following single dose of 40 mg suvorexant; and there was a significant increase on body sway area in the morning following single dose of 20 or 40 mg suvorexant. Night time dosing of suvorexant 30 mg did not result in impairment of balance or psychomotor performance at 4 and 8 hours post-dose as compared to placebo; a small impairment was seen at 90 minutes post-dose.

No effects were seen on measures of sleep onset. Effects were seen on some measures of sleep maintenance following suvorexant discontinuation, but had the characteristics of the return of insomnia symptoms and did not appear to be consistent with clinically meaningful rebound insomnia. No indication of withdrawal was observed in the overall study population based on assessment of patient responses to the Tyrer Withdrawal Symptom Questionnaire or assessment of withdrawal-related adverse events following discontinuation. Suvorexant had no respiratory depressant effect as measured by O<sub>2</sub> saturation.

Cataplexy is a unique safety issue that was investigated due to the theoretical effects of orexin receptor antagonism. The incidence of falls was similar across treatment groups and according to the sponsor none of the falls was related to cataplexy. However, clinical reviewer Dr. Kachi Illoh noted that there was one case of muscle weakness that presents some concern that a narcoleptic process may be associated with trial treatment.

Although the incidence was very low, suicidal ideation occurred more often in patients on suvorexant, especially on high dose suvorexant, than placebo. Also, more patients on suvorexant experienced increased cholesterol levels than placebo, although the increase was small.

Regarding special populations, somnolence events occurred more often in obese patients on high dose suvorexant (13.4% of patients) versus placebo (5.3% of patients). The clinical trials did not identify any differences in clinical safety or efficacy between the elderly and non-elderly in the clinical trials.

### *Efficacy*

Two similarly designed, multinational, randomized, double-blind, parallel-group efficacy studies were conducted in patients with chronic insomnia treated with either suvorexant (at doses of 40 mg, 30 mg, 20 mg or 15 mg) or placebo (N=2030). Suvorexant 40 mg in non-elderly patients (n=451) and suvorexant 30 mg in elderly patients (n=319) were

compared to placebo (n=767) during 3 months of treatment. The recommended dose of suvorexant was superior to placebo on all objective measures of sleep onset and sleep maintenance at Night 1/Week 1, Month 1 and Month 3, except for Latency to onset of Persistent Sleep (LPS) at Month 3 in one study.

### **Agency and Committee Findings**

Clinical reviewer Dr. Kachi Illoh concluded during the Mid-cycle meeting that HD suvorexant showed efficacy based on sleep maintenance endpoints at month 1 and 3 and measures of subjective total-sleep-time (sTST), subjective time-to-sleep-onset (sTSO) and Wakefulness-After-persistent-Sleep Onset (WASO), but “missed” on sleep onset measured as Latency-to-onset-of-Persistent-Sleep (LPS) assessed during the 3 month efficacy and safety study. In terms of safety, Illoh concluded that there was a dose-related risk of somnolence, with a higher risk in females and non-elderly adults. There was also an increased incidence of suicidal ideation, complex sleep-related behavior, sleep onset paralysis, hypnagogic hallucinations and excessive daytime sleepiness (EDS) in HD suvorexant study patients (incidence was generally lower in LD patients). As a result of this safety information, Dr. Illoh recommended that the labeling discuss the avoidance of the use of suvorexant in patients with narcolepsy-like events and suicidal ideation and consideration of periodic monitoring of serum cholesterol levels, especially in those with cardiovascular risk factors.

A meeting of the Peripheral and Central Nervous System Drugs Advisory Committee (PCNS) was convened on May 22, 2013 to discuss the safety and efficacy of suvorexant, including a proposed dosing algorithm for the elderly [15 mg (starting dose)/30 mg (high dose)] and non-elderly [20 mg (starting dose)/40 mg (high dose)] patient populations, and a proposal for 10 mg suvorexant as the lowest effective dose. The committee concluded that the proposed dosing algorithm was effective for the treatment of insomnia characterized by difficulties in sleep onset and/or sleep maintenance, however, the safety for sponsor recommended doses of up to 30 mg (elderly) and 40 mg (non-elderly) had not been established.

The Agency concluded that suvorexant cannot be marketed with an acceptable safety profile without the availability of a 10 mg suvorexant dose, given the risks of next day effects (especially next-day driving impairment) at 15 mg and 20 mg doses. In addition, given the potential for certain relatively large segments of the suvorexant patient population (e.g., obese women and patients taking moderately potent CYP3A4 inhibitors) to experience unacceptably high plasma levels of the drug even at a 10 mg dose, the Agency recommended that the sponsor also produce a 5 mg dose (5 mg and 10 mg suvorexant doses were not available for marketing at the time of Agency review). Finally, the Agency concluded that 30 mg and 40 mg suvorexant doses produce higher risks with little increased benefit, therefore these doses are not recommended.

## **2 DISCUSSION**

Insomnia is a highly prevalent disorder effecting 10-20% of the population<sup>3</sup>, and up to 60% of the growing elderly population suffers from insomnia. About one third of

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<sup>3</sup>Buyse, Daniel J. Insomnia. JAMA 2013;309:706-716.

Americans experience insomnia nightly. Patients may have difficulty with sleep latency, sleep maintenance, and/or sleep quality. Multiple prescription drugs and OTC products are approved to treat insomnia and other prescription drugs such as benzodiazepines, anti-depressants, and anti-psychotics are often used off-label to treat insomnia.<sup>4</sup> There are no drugs currently approved for the treatment of insomnia that have REMS program requirements.

Suvorexant showed clinical benefit in patients with insomnia characterized by difficulties with sleep onset and/or sleep maintenance. The adverse event profile was generally favorable (particularly at the lower doses), and the clinical review team concluded that the benefits of suvorexant appear to outweigh the risks. The serious AEs of concern will be addressed in labeling.

### **3 CONCLUSION**

DRISK believes that a REMS for suvorexant is not necessary at this time. The Applicant's proposal for labeling and routine pharmacovigilance is reasonable. Should DNP identify additional safety information that warrants risk mitigation measures, please send a consult to DRISK.

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<sup>4</sup> *Id.*

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