# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 204569Orig1s000

# MEDICAL REVIEW(S)

# Cross-Discipline Team Leader Review

| | |
|---|---|
| **Date** | June 29, 2013 |
| **From** | Ronald Farkas, MD, PhD |
| **Subject** | Cross-Discipline Team Leader Review |
| **NDA/BLA #** | NDA 204569 |
| **Applicant** | Merck |
| **Date of Submission** | August 29, 2012 |
| **PDUFA Goal Date** | June 29, 2013 |
| **Proprietary Name / Established (USAN) names** | Proprietary name to be determined<br>Established name: suvorexant |
| **Dosage forms / Strength** | 15 mg, 20 mg, 30 mg, 40 mg |
| **Proposed Indication(s)** | Insomnia |
| **Recommended:** | Complete response |

## 1. Introduction

Orexin A and orexin B are hypothalamic neuropeptides that play a critical role in the maintenance of wakefulness. Orexins are also thought to play an important role in modulation of feeding behavior and energy balance. Loss of orexin-containing neurons in humans is associated with narcolepsy, a disease characterized by excessive daytime sleepiness, cataplexy, hypnagogic and hypnopompic hallucinations, sleep paralysis, and other symptoms. Suvorexant antagonizes the two orexin receptors, orexin 1 receptor and orexin 2 receptor. Based on the involvement of orexins in the maintenance of wakefulness, suvorexant was developed by Merck for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance.

Suvorexant is both a new molecular entity and first-in-class.

## 2. Background

In the NDA the sponsor proposed an initial dose of 40 mg for adults, and 30 mg for elderly patients (≥ 65 years of age), taken immediately before bed, with a lower dose of 20 mg for adults and 15 mg for elderly based on individual tolerability. However, during the review cycle, the sponsor informed the Division that, based on public statements made by the Division about the safety of zolpidem products, the sponsor was changing the dosing recommendation to initial dosing with the lower doses above, with the option to increase to the higher doses if necessary for efficacy

Primary clinical review was conducted by Kachi Illoh, MD, and statistical review was conducted by Tristan Massie, PhD. Clinical pharmacology review was conducted by Hristina Dimova, PhD, and pharmacometrics review was conducted by Joo-Yeon Lee. Chemistry review was conducted by Akm Khairuzzaman, PhD., Biopharmaceutics review was conducted by Sandra Suarez, PhD, and drug substance quality aspects were reviewed by Mohan Sapru, PhD. Controlled Substance Staff review was conducted by Chad Reissig, PhD, and Non-Clinical review was conducted by Richard Siarey.

## 3. CMC/Device

Dr. Khairuzzaman found the drug product portion of the NDA to be acceptable, and without need for phase 4 commitments.

Dr. Sapru's review stated that with the exception of a pending issue concerning the control of potential genotoxic impurity (b) (4) the NDA was approvable in terms of drug substance.

Dr. Suarez found that the NDA was acceptable from a biopharmaceutics perspective.

The Office of Compliance issuance of an acceptable recommendation for drug substance manufacturing and testing facilities was pending at the time of this review.

## 4. Nonclinical Pharmacology/Toxicology

Dr. Richard Siarey completed the primary nonclinical review, and Dr. Lois Freed completed a supervisory memo.

Dr. Siarey's overall conclusion was that from a nonclinical perspective, approval of the suvorexant NDA was recommended. However, he found evidence that catapelxy was observed in dogs exposed to MK-4305 (suvorexant) near Tmax, although he concluded that additional information could have been gained by studying the drug in an experimental model that has been used for diagnosing cataplexy in dogs. Dr. Siarey suggested that since cataplexy occurred in dogs near Tmax, a time at which if used for insomnia patients would ordinarily be in bed, safety concern for humans was reduced. Dr. Siarey also found that the neurobehavioral assessment in the pre- and post-natal developmental study was not complete, as the passive avoidance tests was performed too early in development, while learning/acquisition tests and retention/memory tests were not conducted. He recommended that these studies be repeated/conducted.

Dr. Freed agreed that nonclinical studies suggested a theoretical safety concern for cataplexy, concluding that clinical implications, if any, are an issue for the clinical team to decide. She suggested that findings of cataplexy in dog be described in labeling, but would not require additional nonclinical studies of cataplexy, and concluded that the neurobehavioral assessments were sensitive enough to detect at least some adverse effects, and since none were observed, the studies were minimally acceptable. Therefore, the nonclinical team had no suggested post-marketing requirements.

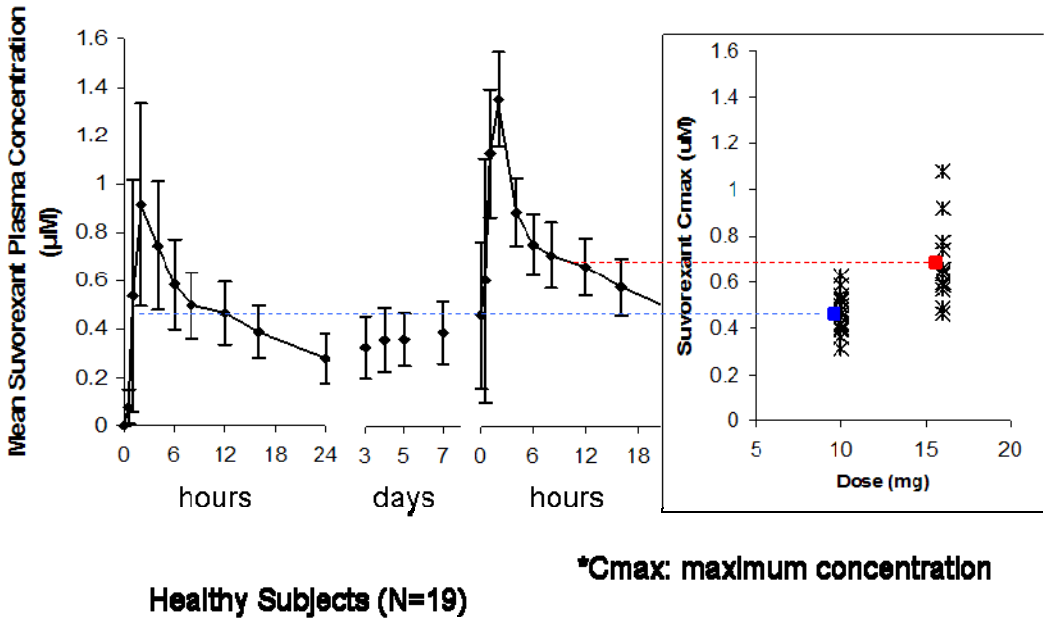
## 5. Clinical Pharmacology/Biopharmaceutics

A single Clinical Pharmacology review combined the findings of Dr. Dimova and Dr. Lee.

*Half life and accumulation*

The half-life of suvorexant is about 12 hours, such that levels accumulate to steady state over several days of dosing.

**Figure 1: Suvorexant PK, 40 mg**




**CDTL: Figure 1 illustrates how the long half-life of suvorexant may impact both safety and efficacy. Suvorexant blood level about 12 hours after a single dose is about the same as the Cmax of a single 10 mg dose (blue dashed line in figure). As discussed below in Section 7, the 10 mg dose appears to be effective for inducing and maintaining sleep. While circadian effects might make patients less sensitive to somnolence during the day versus at night, it is concerning that 'effective' levels are present during the day. With repeat dosing, daytime levels increase due to drug accumulation, such that suvorexant levels about 12 hours after the previous night's dose are similar to Cmax from the 15 mg dose, again a dose found to be effective for sleep latency and maintenance.**

**The long half-life also is likely to affect efficacy, particularly for sleep latency, which is more dependent than sleep maintenance on the time between dosing and blood levels reaching an effective level. At the first dose, suvorexant blood level must go from zero to some level before the drug could be effective. However, with chronic dosing of 40 mg, suvorexant blood level at bedtime, *before* taking that night's dose, is already about the same as Cmax from the 10 mg dose, a dose seemingly effective for sleep latency. This same relationship holds for any dose (with the steady-state suvorexant level proportional to the dose), such that potentially even *if* a low dose (10 mg or even lower) is less effective on night 1 for sleep latency than a high dose, on subsequent nights of chronic dosing, accumulation of suvorexant would allow suvorexant blood levels to more quickly reach an effective level. The difference in efficacy between low and high dose would diminish because, while the high dose would also lead to accumulation of suvorexant, the exposure from the high dose would already have been in or near the plateau region of the dose-response relationship, such that higher exposure would lead to little if any greater efficacy.**

*Intrinsic factors*

Table 1 shows effect of gender and BMI on suvorexant exposure. Exposure is increased in obesity and in women compared to men.

**Table 1: Gender and BMI**

| | reference | test | ratio of exposure metric | |
|---|---|---|---|---|
| **Single Dose** | *non-obese male* | *Obese* male* | AUC | 1.14 |
| | | | Cmax | 1.07 |
| | | | C9 hours | 1.03 |
| | *non-obese female* | *obese female* | AUC | 1.18 |
| | | | Cmax | 1.09 |
| | | | C9 hours | 1.04 |
| **Multiple Dose** | *non-obese male* | *obese male* | AUC | 1.39 |
| | | | Cmax | 1.12 |
| | | | C9 hours | 1.11 |
| | *non-obese female* | *obese female* | AUC | 1.45 |
| | | | Cmax | 1.17 |
| | | | C9 hours | 1.12 |

**Overall female vs male**

| | |
|---|---|
| AUC | 1.17 |
| Cmax | 1.09 |
| C9 | 1.04 |

*Definition of obese (>30 kg/m2)

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