

Testimony to the FDA Peripheral and Central Nervous  
Systems Drugs (PCNS) Advisory Committee

**Suvorexant**  
**(orexin receptor antagonist)**  
**NDA 204-569**

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(We have no financial conflicts of interest)

# Zolpidem: a cautionary tale?

- FDA pre-approval medical review, 1992:
  - “[Preapproval studies] were [consistent] with the conclusion that zolpidem...is not associated with residual effects the next day.”
  - “Except for a finding of slower reaction time for zolpidem 20mg compared to placebo in one of the six studies in non-elderly adults, there was no evidence for next-day decrements in psychomotor function...”

# Zolpidem: a cautionary tale?

- **2008**: Norwegian study of all 3.1 million Norwegians 18-69 years old. Zolpidem/Zopiclone associated with **increased incidence of road traffic accidents** in week following prescription (SIR 2.3 [95% CI: 2.0-2.7] vs. unexposed).

(Gustavsen I, Bramness JG, Skurtveit S, et al. Sleep Med. 2008 Dec;9(8):818-22.)

- **2011**: French study of 72,685 drivers involved in injury-related road traffic accidents in France. **Risk of causing a traffic accident increased** (OR = 2.46 (1.70-3.56)) in those dispensed more than one pill of zolpidem a day during the 5 months before the collision.

(Orriols L, Philip P, Moore N, et al. Clin Pharmacol Ther. 2011 Apr;89(4):595-601.)

- **2013** (May 1<sup>st</sup>): “Sharp rise in emergency department visits involving the sleep medication zolpidem” (SAMHSA)

# Zolpidem: a cautionary tale?

- **2013** (May 14<sup>th</sup>): FDA warns against driving or engaging in “other activities that require complete mental alertness” the day after taking Ambien CR “because zolpidem levels can remain high enough the next day to impair these activities.”
- Half-life:
  - Ambien CR: **2.6 hours**
  - Suvorexant: **12 hours**

# Half-lives of currently marketed insomnia drugs (and suvorexant)

Drug	Half-life (hours)
Quazepam (Doral)*	39
<b>Suvorexant</b>	<b>12</b>
Temazepam (Restoril)*	9
Eszopiclone (Lunesta)	6
Zolpidem (Ambien)	2.6
Zolpidem CR (Ambien CR)	2.6
Triazolam (Halcion)*	1.5 - 5.5
Ramelteon (Rozerem)	1 - 2.6
Zaleplon (Sonata)	1

\*Benzodiazepine

# Suvorexant

- Like other sleep medicines on the market, suvorexant's marginal benefits on sleep latency and maintenance are, in too many cases, achieved at the expense of **prolonged sleepiness**...(and suicidal ideation, hallucinations, elevated cholesterol and possibly cataplexy and sleepwalking)
- Also like its predecessors, long-term dependence ensures chronic effects

Even though suvorexant increases sleep time,  
it makes many patients more sleepy,  
some much sleepier

	Placebo (N=1025)	Low Dose (N=493)	High Dose (N=1291)
Somnolence	3%	7%	11%
Severe Somnolence	0.1%	0.2%	0.6%
Somnolence by age			
>=65 y	3%	5%	9%
<65 y <u>higher</u> dose	3%	8%	13%
Somnolence by sex			
F <u>higher</u> exposure	2%	9%	11%
M	4%	3%	10%

# Daytime Somnolence

- While measures of suvorexant's effectiveness are restricted to only the first 6-9 hours after ingestion, the drug remains "effective" beyond this arbitrary time frame, with dangerous consequences
- Terminal half-life **12 hours** (Ambien CR: **2.6 hours**)
- Slower clearance in women and higher BMI (obese women: clearance **2-3x slower** than normal BMI men)

# Daytime Somnolence

- LD suvorexant more than doubled (6.7 vs. 3.0% placebo) and HD more than tripled (10.7 vs. 3.0%) rates of somnolence in first 3 months of treatment
- HD suvorexant led to **more intense** (0.6 severe vs. 0.1%) and **longer** episodes of somnolence compared with placebo
- More patients on high-dose discontinued due to symptoms (16%; 22/138) than low-dose or placebo patients (6%; 4/64)
- Females especially affected (slower clearance):
  - 8.8% absolute increase in somnolence over placebo vs. 5.9% increase in males

# Excessive Daytime Sleepiness (EDS)

- “uncharacteristic chronic and **persistent** sleepiness during the day, possibly starting as sudden involuntary sleep episodes and occurring throughout the day or over multiple consecutive days.” (p. 209)
  - HD: 1.5% (12/1291; **6 occurred after 3 months**)
  - LD: 0.6% (3/493; none after 3 months)
  - Placebo: 0.3% (3/1025; only 1 after 3 months)
- “[EDS] has safety implications especially when individuals taking the HD have to go about their usual duties **such as driving.**” – Dr. Illoh, Clinical Reviewer (p. 212)

# Somnolence/EDS vs. unrecognized impairment

Definitions of somnolence and EDS in the study depended on an awareness of symptoms. Many with significantly impaired alertness may not be aware of their state and will therefore continue with daily tasks as before, including – critically – driving.

# Driving Impairment

- Two trials (P035 and P039) conducted to evaluate the residual effect of a night-time dose of suvorexant on next-day driving ability
- Hour-long driving tests the morning after dose; standard deviation of lateral position (SDLP) measured lane deviation
- Symmetry analysis suggested excessive lane deviation with both high- **and low-dose** suvorexant
- Five (of only 104) high- **and low-dose** suvorexant subjects (none in placebo or active comparator, zopiclone group) **stopped test prematurely** due to somnolence

# Supervised conditions underestimate real-world impairment

- Studies measured driving performance in supervised, one-hour increments, when patient had been explicitly warned of potential impairment.
- How will a somnolent patient drive in the real-world, alone at the wheel, on longer drives?
- The risks of **falling asleep at the wheel**, much more dangerous than slight lane deviation, could not be measured in these studies. Indeed, subjects could (and 5 on HD did) simply stop the test at the first sign of sleepiness

- 61 year old man, 40 mg AN 07433
  - Difficulty staying awake *while driving*
- 58 year old man, 40 mg AN 03055
  - Strong urges to sleep *while driving*
- 27 year old man, 40 mg AN 03128
  - Severe sleepiness *while driving*
- 60 year old man, 40 mg AN 02615
  - Need to pull over to rest *while driving*

# Suvorexant Low Dose

- 57 year old female, **20 mg** AN0021, study 35
  - “Subject *fell asleep and drove across the middle line with her eyes closed*”
- 69 year old woman, **15 mg** AN11697
  - 2- to 3 hour daily naps; thought she could suffer an accident

# Driving (and other) impairment

- *“...the overall assessment suggests that suvorexant-treated individuals need to avoid driving, operating machinery, or engaging in activities that require full mental alertness until they become fully awake.”*
  - Dr. Illoh (p. 221)
- How will a patient know when they are “fully awake” enough to drive? How many will read the drug label before getting in the car?

# Rebound effects ensure dependence (and chronic risks)

- Even if they had insight into their impaired mental state, dependence may prevent patients from discontinuing the drug
- After discontinuing HD suvorexant and transitioning to placebo, 48.5% of patients achieved less total sleep than before starting the drug, a significantly higher rate than those continuing on placebo (difference 10.8% [95% CI: 5.2, 16.5])

*“Interestingly, the sponsor suggests that rebound effects observed for some sleep maintenance measures do not appear to be consistent with clinically meaningful rebound insomnia. However, I believe that sTST findings for suvorexant, **in both doses** and in the elderly subgroup, **are suggestive of a rebound effect.**”*

- Dr. Illoh (p. 284)

# Suicidal Ideation/Behavior

- In addition, suvorexant seems to cause suicidal ideation and behavior
- 5 in HD group vs. 1 in LD group and 1 in placebo
- Both subjects in LD/placebo groups had prior history of suicidal ideation
- All but one in HD group **had no such history**

# Cholesterol elevations (mg/dL)

- 10mg: +1.2
- 20mg: +2.3
- 40mg: +3.1
- 80mg: +6.0

[Placebo: -3.7]

Dr. Illoh: *“A rise in serum cholesterol levels to the extent found in the Phase 2 trial, up to 6 [mg]/dL difference from placebo, **may not be trivial** especially if maintained over a longer period.”*  
(p. 248)

# Questionable safety of lower doses

Finally, you will be asked today whether a lower dose should be approved as a safer alternative to the high-dose.

## Much less safety data at lower doses

### Phase 3

	Patients	Days	Relative patient days
40 mg (adult)	730	141	5
30 mg (elderly)	627	199	6
20 mg (adult)	353	86	1.4
15 mg (elderly)	202	105	1

### Phase 2

10 mg (adult), 62 patients, 4 weeks

5-6x less safety data for the lower doses when compared with the higher doses

# Questionable safety of lower doses

Especially when considering that the true “low” dose for female and obese patients is unknown and may be much lower than 15mg, this represents a dangerous lack of safety data for lower doses.

Even with the limited data available, however, rates of somnolence were **doubled** in low-dose subjects and driving was significantly impaired on both high- **and low-doses** of suvorexant.

# Questionable safety of lower doses

*“Indeed, if a dosage strength lower than 15 mg is unavailable, **we would need to consider if the drug could be marketed safely at all, if we believe that a substantial proportion of the indicated population needs a lower dose.**”*

- Dr. Katz, Division Director (p. 35)

# Conclusion

- Given plethora of risks, both to patients and the public, suvorexant should not be approved
- Risks evident at lowest dose (15mg) up for approval and amplified in women and obese patients (**terminal half-life 12 hours**)
- Labeling cannot protect patients from risks of which they are not aware (e.g. unconscious mental impairment)
- Dependence potential ensures that many patients will choose to live with side effects than suffer rebound sleep disruption