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**Re: New Drug Application (NDA) 204-569 for suvorexant**

Dear Drs. Katz and Woodcock:

The comments below from Public Citizen’s Health Research Group are being submitted in follow-up to our testimony<sup>1</sup> presented at the May 22, 2013, meeting of the Food and Drug Administration’s (FDA’s) Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee regarding the NDA for the proposed sleep medication suvorexant. We argue in this letter that the FDA should reject the May 22 PCNS Drugs Advisory Committee’s recommendation to effectively approve low-dose suvorexant for the indications of sleep onset and sleep maintenance in patients with sleep disorders because the drug – at both high **and low doses** – poses far too great a risk to both patients and the general public to be on the market.

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<sup>1</sup> Almashat S, Barbehenn E, Carome M, Wolfe S. (Public Citizen’s Health Research Group). Testimony on Suvorexant to the FDA’s Peripheral and Central Nervous System Drugs Advisory Committee. May 22, 2013. <http://www.citizen.org/hrg2129>. Accessed on May 24, 2013.

## I. Overview of arguments against approval

The FDA should not approve suvorexant because the drug's long-lasting risks – both to individual patients and the general public – outweigh any short-term benefits to sleep. 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. Dr. Ronald Farkas, lead medical officer of the Division of Neurology Products, aptly framed the central problem with suvorexant (that is generalizable to all other currently marketed sleep medicines): “Even though suvorexant increases sleep time, it makes many patients *more* sleepy, some *much sleepier*.” [emphasis in original]<sup>2</sup>

This is an adverse event that affects not only the individual patient using the drug but also the health of the general public. Suvorexant's 12-hour half-life (which is longer than all but one of the sleep medications currently on the market), caused next-day driving impairment in pre-approval driving tests when administered in both high and low doses. These findings are ominous considering what we now know about how other nonbenzodiazepine insomnia “z-drugs” affect driving in the real world.

Like its predecessors, the rebound insomnia experienced after discontinuing suvorexant, which occurred in almost half of the subjects on high-dose suvorexant in the pre-approval trials, ensures that too many users will become dependent on the drug in the long-term.<sup>3</sup>

This letter details our arguments against approval of suvorexant.

## II. Next-day somnolence and impairment: A serious public health risk

### *Zolpidem: A cautionary tale?*

There are generally considered to be two categories of sleeping aids: benzodiazepines and nonbenzodiazepine z-drugs. Benzodiazepines were the first generation of sleeping aids and are still sometimes used to help patients sleep. However, the drugs were found to be habit-forming, and their potent and generally longer-lasting sedative effects were associated with an increase in traffic accidents.<sup>4,5,6</sup>

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<sup>2</sup> Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee. Suvorexant (orexin receptor antagonist). May 22, 2013. FDA Briefing Document, p. 396. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM352969.pdf>. Accessed on June 3, 2013.

<sup>3</sup> FDA Briefing Document, p. 279.

<sup>4</sup> Engeland A, Skurtveit S, Mørland J. Risk of road traffic accidents associated with the prescription of drugs: a registry-based cohort study. *Ann Epidemiol.* 2007 Aug;17(8):597-602.

<sup>5</sup> Barbone F, McMahon AD, Davey PG, et al. Association of road-traffic accidents with benzodiazepine use. *Lancet.* 1998 Oct 24;352(9137):1331-6.

<sup>6</sup> Hemmelgarn B, Suissa S, Huang A, et al. Benzodiazepine use and the risk of motor vehicle crash in the elderly. *JAMA.* 1997 Jul 2;278(1):27-31.

Because of these severe side effects, benzodiazepines were gradually phased out as sleeping aids in favor of a new class of nonbenzodiazepine hypnotic medications known as z-drugs. The introduction of this new class of sleeping aids generated hope that these drugs could improve sleep without the deleterious side effects of their benzodiazepine predecessors.

Zolpidem was the first approved z-drug in the U.S., and it is still the most widely used.<sup>7</sup> When the drug came up for approval in 1992, there was no indication that it caused significant next-day impairment. The FDA concluded at the time that the preapproval studies were "... [consistent] with the conclusion that zolpidem ... is not associated with residual effects the next day ..." and that "[e]xcept for a finding of slower reaction time for zolpidem 20 mg [milligram] compared to placebo in one of the six studies in non-elderly adults, there was no evidence for next-day decrements in psychomotor function associated with treatment with zolpidem on the previous night."<sup>8</sup>

These optimistic study assessments were not borne out in practice. In the two decades since zolpidem's approval, at least two large observational studies have concluded that zolpidem increases the risk of car accidents. A 2008 study of all 3.1 million Norwegians ages 18 to 69 found an increased incidence of road traffic accidents in the week following prescription of the z-drugs zolpidem or zopiclone (standardized incidence ratio 2.3 [95% confidence interval (CI): 2.0-2.7] vs. unexposed).<sup>9</sup> A 2011 study of 72,685 drivers involved in road traffic accidents causing injury in France found that the risk of causing a traffic accident more than doubled (odds ratio 2.46 [95% CI: 1.70-3.56]) in those dispensed more than one pill of zolpidem a day during the five months before the collision.<sup>10</sup>

According to *The New York Times*, the FDA had acknowledged receiving approximately 700 reports of "driving mishaps" associated with zolpidem use in its Adverse Event Reporting System as of January 2013.<sup>11</sup> These data prompted the FDA to warn patients not to drive or engage in "other activities that require complete mental alertness" the day after taking extended-release zolpidem (Ambien CR) "because zolpidem levels can remain high enough the next day to impair these activities."<sup>12</sup>

### *Half-life and variable pharmacokinetics*

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<sup>7</sup> Tavernise S. Drug Agency Recommends Lower Doses of Sleep Aids for Women. *New York Times*. January 10, 2013. [http://www.nytimes.com/2013/01/11/health/fda-requires-cuts-to-dosages-of-ambien-and-other-sleep-drugs.html?\\_r=0](http://www.nytimes.com/2013/01/11/health/fda-requires-cuts-to-dosages-of-ambien-and-other-sleep-drugs.html?_r=0). Accessed on May 29, 2013.

<sup>8</sup> Zolpidem Medical Review, p. 39, 41. Drugs@FDA.

[http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/pre96/019908\\_S000\\_MOR.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/019908_S000_MOR.pdf). Accessed on May 29, 2013.

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

<sup>10</sup> Orriols L, Philip P, Moore N, et al. *Clin Pharmacol Ther*. 2011 Apr;89(4):595-601.

<sup>11</sup> *The New York Times*. Drug Agency Recommends Lower Doses of Sleep Aids for Women. Tavernise S. January 10, 2013. <http://www.nytimes.com/2013/01/11/health/fda-requires-cuts-to-dosages-of-ambien-and-other-sleep-drugs.html>. Accessed on June 4, 2013.

<sup>12</sup> FDA Drug Safety Communication. May 14, 2013. <http://www.fda.gov/Drugs/DrugSafety/ucm352085.htm>. Accessed on May 28, 2013.

From a safety standpoint, half-life is the most critical pharmacologic characteristic of sleep medications because it serves as a general marker for the duration of next-day effects. The half-life of extended-release zolpidem, which was the basis for the FDA’s warning against next-day driving due to levels of the drug possibly “remain[ing] high enough to impair these activities,” is 2.6 hours.<sup>13</sup> Suvorexant’s half-life is almost five times greater, at 12 hours.<sup>14</sup>

In fact, if approved, suvorexant’s 12-hour half-life will be longer than all but one of the currently approved sleep medications in the U.S. (see table below). Assuming daily dosing, a half-life of 12 hours means that suvorexant will achieve a steady-state plasma concentration within two to three days (five half-lives). This ensures that suvorexant will remain in the patient’s system constantly throughout the day at both high and low doses. How would the FDA propose protecting patients against next-day somnolence and impairment given the drug’s continuous presence in the body?

Suvorexant’s variable pharmacokinetics in certain patients further exacerbates this danger. Oral clearance is 20 percent slower in women compared with men and the concentration of suvorexant nine hours after dosing (a critical time point for next-day effects) is 20 percent higher in obese patients than in those with normal body mass index and 15 percent higher in the elderly than in the non-elderly. The combination of these factors can dramatically increase next-day blood levels in certain patients. For example, obese women clear the drug two to three times slower than men with normal BMI.<sup>15</sup> Women and obese patients will make up as much as one-third of potential suvorexant users, according to the FDA.<sup>16</sup>

**Table: Half-lives of currently marketed insomnia drugs and suvorexant<sup>17</sup>**

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

\* Benzodiazepines

<sup>13</sup> FDA Briefing Document, p. 57.

<sup>14</sup> FDA Briefing Document, p. 382.

<sup>15</sup> FDA Briefing Document, p. 32.

<sup>16</sup> Verbal statement by FDA officials at PCNS Drugs Advisory Committee meeting, May 22, 2013.

<sup>17</sup> FDA Briefing Document, p. 56-57 (suvorexant, p. 382), and the following drug labels: Rozerem: “Repeated once daily dosing with ROZEREM does not result in significant accumulation owing to the short elimination half-life of ramelteon (on average, approximately 1 to 2.6 hours).”

[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2010/021782s011lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021782s011lbl.pdf). Accessed on May 28, 2013; and Halcion: “Triazolam is a hypnotic with a short mean plasma half-life reported to be in the range of 1.5 to 5.5 hours.” [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2008/017892s038lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/017892s038lbl.pdf). Accessed on May 28, 2013.

*Driving impairment in pre-approval studies*

Because of the post-marketing experience of zolpidem and other z-drugs, potential next-day driving impairment with suvorexant was tested as part of the pre-approval program.

Two small 4-way crossover trials (P035 and P039) were conducted to evaluate the residual effect of a nighttime dose of suvorexant on next-day driving ability.<sup>18</sup> The studies were supervised, hour-long road driving tests conducted the morning after a dose of suvorexant had been given. The primary outcome was a commonly used marker of lane deviation, the standard deviation of lateral position (SDLP), which assessed how often drivers veered from the midline of the road. Symmetry analyses evaluated the proportion of subjects at each dose of suvorexant (and zopiclone, another sleep medicine known to cause driving impairment) who deviated significantly compared with placebo subjects. A SDLP of 2.4 cm was chosen as the cutoff because this represents the SDLP associated with a blood alcohol level of 0.05%,<sup>19</sup> which is above the federal legal limit for commercial drivers (0.04%) and more than half the legal limit for all other drivers over 21 years of age (0.08%) in most states.<sup>20</sup>

Both high- and low-dose suvorexant caused excessive lane deviation as measured by the number of subjects with lane deviation compared with placebo.<sup>21</sup> Significantly more nonelderly subjects and numerically more elderly subjects exhibited excessive lane deviation at the high doses (40 mg and 30 mg, respectively) of suvorexant compared with placebo. Driving impairment with high-dose suvorexant was seen on the morning after the first administered dose and persisted after eight days of continuous dosing. Nonelderly subjects' driving also was impaired at the low dose of 20 mg on the day after the first administered dose.

Dr. Katz concluded in his opening memo to committee members that these study results "... demonstrate that suvorexant can cause significant impairment in driving the morning after dosing."<sup>22</sup> Dr. Illoh, the medical reviewer, concluded that "... 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."<sup>23</sup>

*Real-world implications of next-day impairment and futility of FDA's risk mitigation*

How will these findings translate to the real world? We can extrapolate from empirical data on zolpidem and other z-drugs' association with traffic accidents, but we also can intuit that a drug intended to induce sleep and decrease awareness that stays in the blood at significant levels long after awakening does not bode well for next-day motor function.

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<sup>18</sup> FDA Briefing Document, p. 260-267.

<sup>19</sup> FDA Briefing Document, p. 26.

<sup>20</sup> U.S. Department of Transportation. Commercial Driver's License Program (CDL/CDLIS). Blood Alcohol Content Standards. <http://www.fmcsa.dot.gov/registration-licensing/cdl/cdl.htm>.

<sup>21</sup> FDA Briefing Document, p. 26-29, 33-34.

<sup>22</sup> FDA Briefing Document, p. 33.

<sup>23</sup> FDA Briefing Document, p. 221.

The pre-approval driving studies measured performance in supervised, one-hour increments, when the subject had been explicitly warned of potential impairment.<sup>24</sup> How will a somnolent patient perform in the real world, alone at the wheel, on drives potentially longer than an hour?

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 simply stop the test at the first sign of sleepiness. Three (11 percent) and two (7 percent) of the 28 subjects stopped the test due to self-reported somnolence while on high- and low-dose suvorexant, respectively, while none stopped the test while on zopiclone or placebo.<sup>25</sup>

Dr. Illoh's apt recommendation that patients on suvorexant not engage in driving and other tasks until they become "fully awake"<sup>26</sup> begs the question: How will a patient know when he or she is "fully awake"?

If approved, the FDA would likely opt to mitigate suvorexant's next-day effects using similar post-marketing approaches it has pursued with other z-drugs, in which the FDA relies upon (not very prominent) label warnings alerting patients not to drive or engage in other hazardous occupations the day after taking the drugs.<sup>27,28,29</sup>

For reasons that should be obvious to a public health agency, this approach is guaranteed to fail. For one, labeling cannot protect patients from risks of which they are not aware. Furthermore, although 7-11% of suvorexant users voluntarily stopped the driving test for fear of impairment, the overwhelming majority of those impaired continued with the test. (In the real-world, it is difficult to imagine even 7% of drivers pulling over to the side of the road during their morning commute, especially once they eventually grow accustomed to daily suvorexant-induced drowsiness.)

Even those aware of their impairment will question the feasibility of the FDA's recommendations. With no language in the labels indicating otherwise,<sup>30,31,32</sup> current z-drugs are

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<sup>24</sup> FDA Briefing Document, p. 405 (warning of impairment).

<sup>25</sup> FDA Briefing Document, p. 264.4-way crossover study, so the same 28 subjects received all four interventions at different times.

<sup>26</sup> FDA Briefing Document, p. 221.

<sup>27</sup> Zolpidem/Zolpidem CR label. April 2013.

[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/019908s032s034,021774s013s0151bl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/019908s032s034,021774s013s0151bl.pdf). Accessed on June 4, 2013.

<sup>28</sup> Lunesta label. October 2012. [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/021476s024s0261bl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021476s024s0261bl.pdf). Accessed on June 4, 2013.

<sup>29</sup> Sonata label. April 2013. [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/020859s0131bl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020859s0131bl.pdf). Accessed on June 4, 2013.

<sup>30</sup> Zolpidem indicated for "short-term" use with reference made to clinical studies showing a benefit for "up to 35 days" but no explicit recommendation on timeframe for use. Zolpidem/Zolpidem CR label. April 2013. [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/019908s032s034,021774s013s0151bl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/019908s032s034,021774s013s0151bl.pdf). Accessed on June 4, 2013.

<sup>31</sup> Lunesta label. October 2012. [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/021476s024s0261bl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021476s024s0261bl.pdf). Accessed on June 4, 2013.

commonly used on a daily and indefinite basis. If approved, we assume suvorexant would be similarly used. Does the FDA actually believe that millions of patients will refrain from driving indefinitely? Putting aside the fact that relatively few will have other commuting options to begin with, it strains credulity to expect that even those with the luxury of public transport would permanently upend their daily routines for the sake of an impairment of which they are, in all likelihood, unaware.

### III. Other risks

#### *Suicidal ideation*

Suvorexant appears to cause suicidal ideation in a dose-dependent manner. In the pre-approval trials, suicidal ideation was reported in five subjects taking high-dose suvorexant, compared with only one subject taking low-dose suvorexant and one placebo subject.<sup>33</sup> We note that, while both subjects in the low-dose and placebo groups had a prior history of suicidal ideation, all but one subject taking high-dose suvorexant reported suicidal thoughts **for the first time** while taking the drug. Suicidal thoughts are especially concerning in those with insomnia, a condition often caused by an underlying depression<sup>34</sup> and associated with a higher than average rate of suicides at baseline.<sup>35</sup>

#### *Cholesterol elevations*

Suvorexant caused a dose-dependent increase in total serum cholesterol at all doses of suvorexant administered over the course of the pre-approval trials: 10 mg (+1.2 mg/deciliter [dL]), 20 mg (+2.3), 40 mg (+3.1), and 80 mg (+6.0) compared with a decrease (-3.7 mg/dL) in the placebo group.<sup>36</sup> Dr. Illoh concluded that “a rise in serum cholesterol levels to the extent found in the Phase 2 trial, up to 6 [mg]/dL difference from placebo [for the 40 mg dose], may not be trivial especially if maintained over a longer period.”<sup>37</sup>

### IV. Dependence concerns: Rebound insomnia

Even if patients were to have insight into their impaired mental state, dependence may prevent them from discontinuing the drug, as many subjects who stopped using suvorexant experienced even worse sleep disturbances than they did before being placed on the drug. After discontinuing high-dose suvorexant and transitioning to placebo, 48.5% of patients achieved less total sleep

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<sup>32</sup> Sonata label. April 2013. [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/020859s0131bl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020859s0131bl.pdf). Accessed on June 4, 2013.

<sup>33</sup> FDA Briefing Document, p. 205-207.

<sup>34</sup> Estroff Marano H. Bedfellows: Insomnia and Depression. Psychology Today. July 1, 2003.

<http://www.psychologytoday.com/articles/200307/bedfellows-insomnia-and-depression>. Accessed on June 4, 2013.

<sup>35</sup> Pigeon WR, Pinquart M, Conner K. Meta-analysis of sleep disturbance and suicidal thoughts and behaviors. *J Clin Psychiatry*. 2012 Sep;73(9):e1160-7.

<sup>36</sup> FDA Briefing Document, p. 248.

<sup>37</sup> FDA Briefing Document, p. 248.

than before starting the drug, a significantly higher rate than those continuing on placebo (difference 10.8% [95% CI: 5.2, 16.5]).<sup>38</sup> Dr. Illoh concluded that, “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 [total sleep time] findings for suvorexant, **in both doses** and in the elderly subgroup, are suggestive of a rebound effect.” Due to these rebound effects, patients on suvorexant are likely to become dependent on the drug over time, making it difficult to discontinue therapy even if side effects became severe.

## V. Clinical relevance of efficacy claims

Given these severe risks to both patients and the public, the efficacy claims of suvorexant must be scrutinized. Efficacy of suvorexant on both sleep latency and sleep maintenance were measured in two Phase 3 trials.

On sleep latency, pooled results from the two trials indicated that high-dose suvorexant decreased the time to sleep onset subjectively by 11 minutes and objectively by six minutes by the third month of treatment.<sup>39</sup> However, significant improvement in objective sleep onset was only seen in one of the two trials at three months. The efficacy of low-dose suvorexant on sleep latency was much more inconsistent, with subjects on low-dose suvorexant falling asleep more quickly by 5-7 minutes subjectively and 0.3-8 minutes objectively compared with placebo after three months of treatment. Yet these improvements were borderline or statistically insignificant on three of the four measures of sleep onset across both trials.<sup>40</sup>

Regarding sleep maintenance, high-dose and low-dose suvorexant increased total sleep time by 22 minutes and 16 minutes, and reduced objective wakefulness after sleep onset (WASO) by 26 minutes and 23 minutes, respectively.<sup>41</sup> However, the reduction in subjective WASO (sWASO, which is patients’ perceptions of the frequency of middle-of-the-night awakenings) with low-dose suvorexant was not significant in one Phase 3 trial, and this outcome was not tested with the low dose in the other Phase 3 trial. The FDA “... had previously requested sWASO as a key sleep maintenance endpoint.”<sup>42</sup>

In an eight-hour night, these findings — especially at the lower doses — represent modest improvements and are in line with the trend seen with other sleep medicines. A 2012 meta-analysis of all Phase 2 and 3 studies conducted of approved sleep medicines found an average decrease in sleep latency of only 22 minutes over placebo, with no significant benefits seen on

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<sup>38</sup> FDA Briefing Document, p. 279.

<sup>39</sup> FDA Briefing Document, p. 135.

<sup>40</sup> FDA Briefing Document, p. 7-10. P-values for month 3: LD vs. Placebo for sTSO and LPS.

<sup>41</sup> FDA Briefing Document, p. 134.

<sup>42</sup> FDA Briefing Document, p. 134.



measures of sleep maintenance, including total sleep time.<sup>43</sup> It should be noted that this meta-analysis included studies testing higher doses of certain drugs (e.g., zolpidem) that the FDA no longer recommends for most patients.<sup>44</sup> The fact that no increase in the amount of sleep has been consistently demonstrated, even at higher doses, offers a revealing insight into the true value of these drugs for patients whose principal complaint is a lack of sleep. This is not to discount the marginal benefit on sleep latency, but rather to contextualize the efficacy claim in light of the grave risks of the drugs.

Insomnia is a complex and multi-faceted condition. While the disease is characterized by a lack of sleep or prolonged sleep onset, the most important metric when analyzing treatments is how people feel *while awake*. Suvorexant does help some people with insomnia get to sleep a bit more quickly and stay asleep for a few minutes longer, but at the cost, in too many cases, of next-day somnolence and driving impairment (not to mention a laundry list of other potentially fatal side effects).

## VI. Misguided focus on dosage approval

At the PCNS Drugs Advisory Committee meeting, the FDA seemed to favor approving the lower doses studied in the Phase 3 trials (15 mg and 20 mg for elderly and nonelderly patients, respectively), arguing that these doses were safer and as effective as the higher doses (30 mg and 40 mg, respectively). (Highlighting the FDA's zeal, apparent during the meeting, to approve a lower dose, agency officials openly considered approving a 10-mg dose based solely on data from 57 subjects in a Phase 2 trial.<sup>45</sup> A bizarre scene then unfolded whereby FDA officials insisted that a 10-mg dose was effective over the objections of the manufacturer, which presumably wanted to avoid the possibility of a pre-approval requirement to study the dose in a larger Phase 3 trial.)

The committee eventually concurred with the FDA's apparent preference, overwhelmingly approving the lower doses while voting 8-7 that the higher doses were not safe.<sup>46</sup> The committee's vote in favor of the lower doses ignored the inconsistent, more modest efficacy findings and the significant next-day driving impairment, cholesterol elevations, and rebound insomnia seen with the lower doses. In addition, because of suvorexant's unpredictable pharmacokinetics and unusually long half-life, a low dose for some is high for others, such as

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<sup>43</sup> Huedo-Medina TB, Kirsch I, Middlemass J, et al. Effectiveness of non-benzodiazepine hypnotics in treatment of adult insomnia: meta-analysis of data submitted to the Food and Drug Administration. *BMJ*. 2012 Dec 17;345:e8343.

<sup>44</sup> FDA Drug Safety Communication. May 14, 2013. <http://www.fda.gov/Drugs/DrugSafety/ucm352085.htm>. Accessed on May 28, 2013.

<sup>45</sup> Verbal statement by Dr. Katz at PCNS Drugs Advisory Committee meeting May 22, 2013. FDA Briefing Document, p. 64 (57 subjects on 10-mg dose).

<sup>46</sup> Grogan K. FDA panel backs Merck & Co sleep drug but at low doses. May 23, 2013. *PharmaTimes*. [http://www.pharmatimes.com/Article/13-05-23/FDA\\_panel\\_backs\\_Merck\\_Co\\_sleep\\_drug\\_but\\_at\\_low\\_doses.aspx](http://www.pharmatimes.com/Article/13-05-23/FDA_panel_backs_Merck_Co_sleep_drug_but_at_low_doses.aspx). Accessed on June 6, 2013.

women and obese patients (who make up as much as one-third of potential users of the drug, according to the FDA<sup>47</sup>).

Even if the low dose were safe, however, the fixation on which dose to approve becomes largely immaterial when considering how this medicine will actually be used in the real world. Despite the evident concerns among FDA reviewers and committee members about the safety of the higher doses and the effectiveness of the lower doses, both seemed to favor a “start low, go slow” approach in which physicians would be advised to begin with the low doses but, if ineffective, could progress to higher ones. However, the inconsistent efficacy results of low-dose suvorexant on sleep latency and sWASO raise concerns as to how many patients will ultimately end up on the higher doses that FDA reviewers and committee members both consider dangerous.

The inconsistent efficacy of low-dose suvorexant on sWASO is of particular concern. Advisory committee member and sleep expert Dr. Christian Guilleminault reminded the panel that it was fairly common for patients on sleep medications to take more than the prescribed dosage following repeated awakenings in the middle of the night.<sup>48</sup> Thus, taking a second, low-dose suvorexant in the middle of the night (closer to the morning commute) will not be an uncommon phenomenon.

All of these considerations make it clear that a large number of patients will be exposed to high doses of suvorexant, with all of the associated adverse events – including dangerous driving impairment – regardless of the dose ultimately approved.

## **VII. False hope, real dangers**

We cannot urge the FDA more strongly to reject the NDA for suvorexant. The advisory committee’s failure to recognize the dangers posed by this latest sleep medicine should not obligate the FDA to follow suit. Approving suvorexant would run counter to the FDA’s welcome (though belated) recent push to minimize the now universally recognized public health consequences of the overuse of sleep medications, such as zolpidem. The agency should instead redouble its efforts to re-examine not only higher doses but *all* overuse of hypnotics in the treatment of insomnia. The inevitable direct-to-consumer marketing blitz following suvorexant’s approval would exacerbate already-epidemic sleep medication overuse while providing yet more false hope to patients with such a pervasive and complex condition.

Thank you for taking our comments into consideration.

Sincerely,

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<sup>47</sup> Verbal statement by FDA officials at PCNS Drugs Advisory Committee meeting, May 22, 2013.

<sup>48</sup> Verbal statement by Dr. Guilleminault at PCNS Drugs Advisory Committee meeting, May 22, 2013.

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