Belsomra Safety and Efficacy

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OND/CDER/FDA
• Safety concerns
• Objective efficacy results
Key Safety Concerns

- Daytime somnolence can be severe and occur suddenly: *patients drive while impaired*
- Unconscious nighttime activity
- Suicidal ideation

- Other narcolepsy-associated events
  - Sleep paralysis, hypnagogic hallucinations, mild cataplexy
Daytime Somnolence

Even though suvorexant increases sleep time, many patients **more** sleepy during day, some **much sleepier** : Dose-related

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=1025)</th>
<th>Low Dose (N=493)</th>
<th>High Dose (N=1291)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>3%</td>
<td>7%</td>
<td>11%</td>
</tr>
<tr>
<td>‘Excessive daytime sleepiness’</td>
<td>0.2%</td>
<td>0.6%</td>
<td>1.1%</td>
</tr>
</tbody>
</table>

- Sponsor defined: beyond potential residual drug effect
- Persistent, recurrent, impairing, may be sudden, involuntary
Patients were unable to avoid driving in the suvorexant studies while seemingly impaired by excessive daytime sleepiness, despite close clinical monitoring and warnings about possible impairment.

- “MK-4305 may make you sleepy”

- “Your ability to drive or operate other heavy machinery may be impaired after taking study drug”
If warnings not effective in study, how will drug be used safely in clinical setting?

Increased FDA understanding that patients are *not* reliably aware of drug impairment...

...and even *if* aware, may still drive
## Driving Study Findings

<table>
<thead>
<tr>
<th></th>
<th>Adult (&lt;65 years)</th>
<th>Elderly (≥ 65 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First night/day</td>
<td>20 mg</td>
<td>15 mg</td>
</tr>
<tr>
<td></td>
<td>40 mg</td>
<td>30 mg</td>
</tr>
<tr>
<td>After 1 week</td>
<td>20 mg</td>
<td>15 mg</td>
</tr>
<tr>
<td></td>
<td>40 mg</td>
<td>30 mg</td>
</tr>
</tbody>
</table>

- Statistically significant impairment
- ‘Lean’ towards significant impairment → worrisome in small safety study
Unconscious Nighttime Behavior

65 year old man

- During PSG recording, 2.5 hours after dosing
- Talking in sleep, sat up in bed, went back to sleep
- Lunged out of bed, and hit his head and face against a wall

- Sleep walking event after 2 weeks off drug
- Past history of sleep talking, not sleep walking

Concerning to see this type of event in relatively small number of exposed patients
Suicidal Ideation

- Suicidal ideation assessed prospectively with questionnaire
  - Placebo: 0.1% 1 patient
  - Low dose: 0.2% 1 patient
  - High dose: 0.7% 9 patients

- Ideation generally ‘mild’, but still thought to indicate increased risk of suicide
- Patients had prior history and/or ongoing psychosocial stress…
- Still consistent with drug-related adverse effect in patients with baseline risk factors
Efficacy
Subjective Sleep Time

- Known (and shown in Belsomra studies) to be inaccurate; even less accurate because of some drugs, potentially including Belsomra

- Sleep might be misperceived as longer due to non-beneficial or even adverse drug effect

- Potentially meaningful, but interpret with caution
Sleep Maintenance
No Clear Exposure/Efficacy Relationship

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 28</th>
<th>Day 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median: AUC0-24 (uM/hr)</td>
<td>PL 5 7 9 10 12 16 PL 6 9 11 13 15 20 PL 6 9 11 13 16 20</td>
<td></td>
</tr>
<tr>
<td>change from baseline in WASO (min)</td>
<td>change from baseline in WASO (min)</td>
<td>change from baseline in WASO (min)</td>
</tr>
</tbody>
</table>

AGE_group
<65 >=65
Sleep Onset

No Clear Exposure/Efficacy Relationship

change from baseline in LPS (min)

Median: PL 5 7 9 10 12 16 PL 6 9 11 13 15 20 PL 6 9 11 13 16 20
AUC(uM*hr)

AGE_group
- <65
- >=65
Conclusions

- Major safety concerns
  - Daytime somnolence
  - Impaired driving
  - Unconscious nighttime behaviors
  - Suicidal ideation
  - Narcolepsy-like syndrome
Conclusions

- Potentially serious adverse effects clearly dose-related
- Patients can’t reliably respond to their own risk from drug
- No clear efficacy decrease down to, and including, 10 mg
- Risk/benefit balance might be better even if less than maximum efficacy at doses lower than 10 mg
- No apparent justification for using higher doses of insomnia drug than necessary for efficacy