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APPLICATION NUMBER:

204569Orig1s000

OTHER ACTION LETTERS



NDA 204569

COMPLETE RESPONSE

Merck & Co., Inc.
126 Lincoln Avenue
P.O. Box 2000, RY 33-208
Rahway, NJ 07065

Attn: Nadine Margaretten, Ph.D.
Director, Worldwide Regulatory Affairs

Dear Dr. Margaretten:

Please refer to your New Drug Application (NDA) dated August 30, 2012, received August 30, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Suvorexant (MK-4305) 15, 20, 30 and 40 mg oral Tablets.

We acknowledge receipt of your amendments dated:

September 21, 2012, October 4, 2012, November 2, and 20, 2012, December 7, 12, 17, 20 and 21, 2012, January 17, 2013, February 5 and 28, 2013, March 11, 27, and 29, 2013, April 9, 11, 12, 19, 23, and 29, 2013, May 22 and 31, 2013, and June 5, 2013.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

EFFECTIVENESS

We have concluded that you have submitted substantial evidence of effectiveness for suvorexant for the treatment of insomnia characterized by difficulty with sleep onset and/or sleep maintenance, at doses of 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 80 mg.

We have concluded that the 10 mg dose, although evaluated in Study 006 in only a limited number of subjects, is effective in reducing sleep latency and increasing sleep maintenance, based on objective measures. Although subjective measures did not reach statistical significance, pharmacometric analyses have demonstrated that for the range of plasma levels achieved at doses from 10 to 80 mg, there is little difference in efficacy measured by objective sleep maintenance and sleep latency. Taken together, these data confirm that, at least for some patients, 10 mg is an effective dose.

At their meeting on May 22, 2013, the Peripheral and Central Nervous Systems Advisory Committee endorsed our view that the lowest effective dose of suvorexant should be

recommended, at least as a starting dose, in product labeling. In addition, the Committee recommended that further study of the 10 mg dose was not necessary, primarily because they had concluded that the 10 mg dose had already been shown to be effective.

Note also that whereas no single dose was studied in both elderly patients (age 65 years and over) and non-elderly adults (age 18 to 65 years), we conclude that doses from 10 to 40 mg are effective in both elderly and non-elderly adult patients.

SAFETY

We conclude that you have not demonstrated that suvorexant is safe for use, even at the revised lower doses you proposed on May 14, 2013: 15 mg for elderly patients and 20 mg for non-elderly adult patients. Specifically, for reasons described below, we conclude that suvorexant has not been demonstrated to be adequately safe even if the starting dose is 15 mg for both non-elderly and elderly adult patients.

We find that suvorexant is associated with a dose-related risk of the following potentially serious and life-threatening adverse effects:

- suicidal ideation
- daytime functional impairment and associated increased risk of motor vehicle accidents
- unconscious nighttime activity
- a narcolepsy-like syndrome including cataplexy-like events
- hallucinations and sleep paralysis.

Suicidal Ideation

At doses of 30 and 40 mg, there was a several-fold increase in suicidal ideation versus placebo. Based on this adverse effect alone, we have serious concerns about the safety of the 30 and 40 mg doses, especially in the context of the benefit demonstrated in insomnia.

Relatively few patients were exposed at the 15 and 20 mg doses, about 550 patients, and the duration was relatively short, about 3 months. Thus, there was limited ability to characterize the risk of suicidal ideation at the lower doses studied.

Daytime Impairment

Because of drug-related daytime functional impairment and risk of motor vehicle accidents, we conclude that the available data are not adequate to support the safety of the 15 mg dose of suvorexant, at least as the starting dose. The study of driving impairment of 20 mg suvorexant in adults showed impairment in driving skills, such as ability to maintain lane position. Although the 15 mg dose did not demonstrate impairment in a driving study, there is considerable overlap in exposure from 15 mg and 20 mg doses (particularly for patient subgroups with increased suvorexant exposure, such as obese patients), such that a sizable proportion of adults who take 15 mg suvorexant would likely experience functional impairment similar to that caused by the 20 mg dose. Furthermore, analyses of adverse events suggest dose-related somnolence and inability to resist falling asleep while driving (including microsleep), even at a dose as low as 15 mg.

Finally, patients are not necessarily aware of their own impairment, suggesting that adverse events reports could underestimate the actual risk.

Unconscious Nighttime Activity

Two patients on suvorexant vs. none on placebo experienced unconscious, out-of-bed nighttime activity, including a 65 year-old man on the 30 mg dose who lunged out of bed and hit his face against a wall. Potentially similar types of adverse events caused by other insomnia drugs, called 'complex sleep-related behaviors,' are thought to be very rare, and to occur mainly in the setting of higher than recommended doses and use with alcohol. Clearly these were not factors in this patient, given that the event occurred during an inpatient sleep study. With so few events, the drug-relatedness of these events is uncertain, but nevertheless concerning. We do not believe the 30 and 40 mg doses can be considered adequately safe without better characterization of the risk of unconscious nighttime behaviors, and as noted above, with relatively few patients exposed at the 15 and 20 mg doses, there is some uncertainty whether this risk is acceptable even at these doses.

Narcolepsy-like Syndrome

We also conclude that suvorexant is associated with a narcolepsy-like syndrome, including excessive daytime sleepiness, hallucinations, sleep paralysis, and cataplexy-like events. We believe there are multiple events of leg weakness in patients on the 30 mg, 40 mg, and higher doses of suvorexant that are similar to cataplexy. You appear to dismiss the possibility that these events reflect cataplexy because of the absence of a clear emotional trigger, but even in idiopathic narcolepsy, cataplexy can occur without an identifiable emotional trigger (or any other trigger, such as surprise or sudden physical activity). In any case, cataplexy-like events of concern from suvorexant might differ in some ways than similar events in narcoleptic patients. Whereas falls or injuries from these events were not reported in suvorexant studies, we remain concerned that risk of falls from these events has not been adequately investigated to permit approval of the 30 and 40 mg doses.

Hallucinations and Sleep Paralysis

We are also concerned that hallucinations and sleep paralysis, which were reported more frequently in patients taking suvorexant than placebo, can cause clinically meaningful psychological harm in patients with insomnia. Such events can be terrifying, and increase anxiety associated with sleep, exacerbating the underlying insomnia.

Additional Concerns

The patient population for suvorexant may be at a higher risk from the above adverse effects than the study population because of increased prevalence and severity of concomitant disease (e.g. depression, obesity, undiagnosed obstructive sleep apnea, parasomnias, etc.) and concomitant medication use (e.g., antidepressants, central nervous system depressants) with potentially additive or even synergistic adverse interactions with suvorexant. Based on experience with other insomnia drugs, there is reason to believe this will be true.

Benefit-Risk Assessment

We conclude that the 10 mg dose of suvorexant, but not the 15 mg dose, is effective and presents acceptable risk as a starting dose for patients with insomnia. Thus, the 10 mg dose must be available at the time of approval. Because manufacturing data necessary to support approval of a 10 mg dosage form have not been submitted, we cannot approve the suvorexant NDA in its present form.

Furthermore, certain patients are expected to have significantly higher plasma levels of suvorexant (e.g., patients taking concomitant CYP3A4 inhibitors). For such patients, the 10 mg dose is predicted to be excessive. For this reason, you must produce a 5 mg dosage strength. This dose would be expected to produce plasma levels in patients taking moderately potent CYP3A4 inhibitors similar to those produced by the 10 mg dose in other patients.

We believe that labeling can be written to allow safe use of the 15 mg and 20 mg doses in patients in whom the 10 mg dose is well tolerated but not effective. However, we conclude that the 30 and 40 mg doses are unlikely to be safe even when used in this way.

LABELING

Submit draft labeling that incorporates revisions in the attached labeling. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations that support any proposed changes.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
 4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
 5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
 6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
 7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
 8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Cathleen Michaloski, BSN, MPH, Sr. Regulatory Project Manager, at (301) 796-1123.

Sincerely,

{See appended electronic signature page}

Ellis F. Unger, M.D.
Director, Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE
Labeling

17 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELLIS F UNGER
06/28/2013