Office Director Decisional Memo

Date	13 August 2014
From	Ellis F. Unger, MD Director, Office of Drug Evaluation 1
Subject	Office Director Decisional Memo
NDA	204569
Applicant Name	Merck & Co., Inc.
Date of Submission	14 February 2014
PDUFA Goal Date (post-extension)	14 August 2014
Proprietary Name / Established (USAN) Name	Belsomra Suvorexant
Dosage Forms / Strength	Tablets, oral: 5, 10, 15, and 20 mg.
Proposed Indication(s)	Insomnia characterized by difficulty falling asleep and/or staying asleep
Action:	**Approval**

Material Reviewed/Consulted	**Names of discipline reviewers**
Clinical	Kachikwu Illoh, Ronald Farkas, Eric Bastings
Biostatistics	Tristen Massie, Ling Chen, Kun Jin
Pharmacology/Toxicology	Richard Siarey, Paul Brown, Lois Freed
ONDQA Biopharmaceutics	Sandra Suarez, Angelica Dorantes, Richard Lostritto
Clinical Pharmacology /Biopharmaceutics	Hristina Dimova, Angela Men, Xinning Yang
Pharmacometrics	Joo-Yeon Lee, Satjit Brar, Atul Bhattaram
Methods Validation	Michael Trehy
Chemistry Manufacturing Controls (CMC)	Akm Khairuzzaman, Mohan Sapru, Martha Heimann, Ramesh Sood
Statistical Review – Carcinogenicity Study	Tristan Massie, Kun Jin, Kooros Mahjoob, Mohammad Atiar Rahman, Karl Lin
Office of Prescription Drug Promotion	Melinda McLawhorn
Office of Manufacturing and Product Quality	Akm Khairuzzaman, Mohan Sapru, Ramesh Sood
Division of Scientific Investigations	Antoine El Hage, Susan Thompson
Division of Medication Error Prevention and Analysis, Office of Surveillance and Epidemiology	Jacqueline Sheppard, Julie Neshiewat, Irene Z. Chan, Kellie Taylor, Carol Holquist, Tingting Gao
Patient Labeling	Twanda Scales, LaShawn Griffiths, Melissa Hulett, Melinda McLawhorn
Risk Evaluation and Mitigation	Nyedra Booker, George Neyarapally, Kendra Worthy, Claudia Manzo
Controlled Substance Staff	Chad J. Reissig, Michael Klein, Silvia Calderon
QT/IRT	Janice B. Brodsky, Joanne Zhang, Jee E. Lee, Kevin M. Krudys, Norman Stockbridge
Cross-Discipline Team Leader	Ronald Farkas
Division of Pulmonary, Allergy, and Rheumatology Products Consult	Lydia Gilbert-McClain
Labeling Review	Nicole Bradley
Regulatory Project Manager	Cathleen Michaloski
Deputy Director, Division of Neurology Products	Eric Bastings

Background: This NDA is for suvorexant, an orexin receptor antagonist, indicated for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance. On June 28, 2013, we issued a complete response (CR) letter for this application for reasons explained below.

The applicant originally proposed suvorexant starting doses of 20 or 40 mg for non-elderly adults, and 15 or 30 mg for elderly adults, with the higher doses recommended. The Division enumerated a number of concerns regarding use of the higher doses in the FDA Briefing Package in advance of the May 22, 2013, Peripheral and Central Nervous System Advisory Committee Meeting, and the applicant responded with a proposal for a new, lower initial dosing recommendation: 20 mg for non-elderly adult patients and 15 mg for elderly patients.

Although the Division appreciated the applicant's willingness to lower the recommended doses, concern remained by some on the review team that the starting dose remained higher than necessary. Given that next-morning somnolence and other side effects have repeatedly been shown to be dose-related, they considered it important to identify the lowest effective dose of a sleep drug, and I agree with that view.

The data suggested that a 10-mg starting dose would be sufficient for many patients. The exposure-response data showed that exposure with the 10- and 15-mg doses was not importantly different. For the 10-mg dose, there were statistically significant improvements in objective measurements of sleep latency and sleep maintenance in Study 6. Although improvements in subjective total sleep time and subjective time to sleep onset with the 10-mg dose were not statistically significantly different from placebo in Study 6, relatively few subjects were tested at the 10-mg dose, so that statistical significance would not have been expected.

The data supporting efficacy for the 10-mg dose and the growing recognition that individual patients may respond differently to a particular dose provided the impetus to approve a 10-mg starting dose, acknowledging that dosing will need to be individualized and will need to be higher for some patients. We thought the 10-mg dose would also provide additional safety for special populations – patients taking moderate CY3A4 inhibitors and patients with moderate hepatic impairment – as well as women, obese patients, and obese women; the clearance in obese women is 1/2 to 1/3 that in men with a normal body mass index (BMI). In addition, because we expected that certain segments of the population may have unacceptably high plasma levels even with the 10-mg dose (for example, obese women and patients taking moderate CYP3A4 inhibitors), we recommended that the applicant also produce a 5-mg dosage strength, a strength that would be expected to yield plasma levels in these populations that are essentially equivalent to the 10-mg dose in other populations.

At the time of the last submission, manufacturing data necessary to support approval of 5- and 10-mg tablets were not available; therefore, the application could not be approved and we took a Complete Response action.

The submission under review is a complete response to the CR letter, consisting primarily of CMC/biopharmaceutics and clinical pharmacology information to support the 5-mg and 10-mg tablets. The applicant also included the results of new nonclinical toxicity studies.

CMC/Biopharmaceutics: The CMC review concluded that manufacturing of the drug product and drug substance are acceptable. The new lower strengths (5 mg and 10 mg) are manufactured (b) (4) the quality of which was found to be acceptable

during the first review. (b) (4) Manufacturing site inspections were acceptable. There are no outstanding CMC issues.

Biopharmaceutics: The dissolution profiles for two additional batches per strength for the new 5 mg and 10 mg dosage forms were found to be adequate to support approval.

Clinical Pharmacology: The submission contains two new relative bioavailability studies, P055 and P056. They show similar pharmacokinetics between four 5-mg tablets and one 20-mg tablet of suvorexant, and between two 10-mg tablets and one 20-mg tablet of suvorexant. The data were found adequate to support the approval of 5-mg and 10-mg tablets.

Clinical/Statistical-Efficacy: No new efficacy data considered to be needed and none were submitted.

Safety: No new safety data were included in this submission. The sponsor has withdrawn the 30- and 40-mg dosage strengths from the Dosage and Administration section of labeling.

Advisory Committee Meeting: An advisory meeting was held May 22, 2013. A second advisory committee meeting was not needed for this application.

Pediatrics: Pediatrics is discussed in detail by Dr. Farkas in his first cycle CDTL memo. As discussed by Dr. Farkas, a full waiver for pediatric studies is being issued.

Decision/Action/Risk Benefit Assessment:

As the applicant has provided adequate CMC/Biopharmaceutics and Clinical Pharmacology information to support approval of the 5- and 10-mg dosage strengths, which were found to constitute safe and effective starting doses in the first cycle (with the 5-mg dose to be used in patients taking concomitant CYP3A4 inhibitors).

This NDA will be approved with the labeling as per the approval letter.

Of note, many labels for sleep drugs do not provide the actual efficacy data, and we are including the primary objective and subjective endpoint data in section 14 of the package insert.

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/s/

ELLIS F UNGER
08/13/2014