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APPLICATION NUMBER:

204569Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Eric Bastings, MD. Deputy Director.
Subject	Division Summary Review
NDA/BLA #	204,569
Applicant Name	Merck & Co., Inc.
Date of Submission	February 14, 2014
PDUFA Goal Date	August 14, 2014
Proprietary Name / Established (USAN) Name	Belsomra/Suvorexant
Dosage Forms / Strength	Tablets: 5, 10, 15, and 20 mg
Proposed Indication(s)	Treatment of insomnia characterized by difficulty falling asleep and/or staying asleep
Recommended Action	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Pharmacology Toxicology Review	Richard Siarey, Ph.D.
CMC Review	Akm Khairuzzaman, Ph.D.
Clinical Pharmacology Review	Hristina Dimova, Ph.D.
Biopharmaceutics	Sandra Suarez Sharp, Ph.D.
CDTL Review	Ronald Farkas, MD, Ph.D.
OSE/DMEPA	Jacqueline Sheppard, Pharm.D.
Patient Labeling	Twanda Scales, RN, MSN/Ed

OND=Office of New Drugs
OSE=Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
CDTL=Cross-Discipline Team Leader

1. Introduction and Background

On August 30, 2012, the applicant was issued a complete response (CR) letter to their NDA for suvorexant, a selective antagonist of orexin receptors OX1R and OX2R.

In the first cycle, FDA concluded that the applicant had 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 to 80 mg. FDA also found suvorexant to be associated with a dose-related risk of suicidal ideation, daytime functional impairment, unconscious nighttime activity, narcolepsy-like syndrome including cataplexy-like events, hallucinations, and sleep paralysis. Because of that risk, FDA considered critically important to identify and use the lowest effective dose of suvorexant as the starting dose, and found 10 mg (or 5 mg in patients taking concomitant CYP3A4 inhibitors) to be effective and present an acceptable risk as a starting dose (instead of a 20 mg dose in non-elderly adults and a 15 mg dose in elderly adults, as proposed by the applicant). Because manufacturing data necessary to support approval of a 5 mg and 10 mg tablet were not available, the application could not be approved in the first cycle.

In addition, the applicant proposed doses up to 40 mg in non-elderly adults and 30 mg in elderly adults. The review team had safety concerns about these higher doses, but considered doses of up to 20 mg as adequately safe if used in patients in whom the 10 mg dose is well tolerated but not effective.

The submission under review is a complete response to the CR letter. It consists primarily in 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.

2. CMC/Biopharmaceutics

I concur with the conclusions reached by Dr. Khairuzzaman, chemistry reviewer, regarding the acceptability of the manufacturing of the drug product and drug substance. Dr. Khairuzzaman notes that the new two lower strengths (5 mg and 10 mg) are manufactured (b) (4) , the quality of which was acceptable during the first review cycle. (b) (4) Manufacturing site inspections were acceptable. Stability testing supports an expiry of 36 months for 15 mg and 20 mg tablets, and 12 months for 5 mg and 10 mg tablets. There are no outstanding issues.

I concur with the conclusions reached by Dr. Sharp, Biopharmaceutics reviewer, that there are no outstanding biopharmaceutics issues that preclude approval. Dr. Sharp reviewed the dissolution profile for two additional batches per strength for the new 5 mg and 10 mg dosage forms, and found these data adequate to support approval of these new dosage strengths.

3. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by Dr. Siarey, pharmacology/toxicology reviewer, that there are no outstanding pharm/tox issues that preclude approval.

4. Clinical Pharmacology

I concur with the conclusions reached by Dr. Dimova, clinical pharmacology reviewer, that there are no outstanding clinical pharmacology issues that preclude approval.

Dr. Dimova notes that the submission contains two new relative bioavailability studies (Study P055 and P056). Study P055 and P056 respectively 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. Dr. Dimova finds these data adequate to support the approval of 5 mg and 10 mg tablets, on a clinical pharmacology standpoint.

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical-Efficacy

No new efficacy data were included in this submission. In the first cycle, suvorexant was found to be effective 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.

7. Safety

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

8. Advisory Committee Meeting

An advisory meeting was held in the first cycle. No new advisory meeting is needed for this application.

9. 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 should be issued.

10. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

11. Labeling

The proprietary name proposed by the applicant, Belsomra, was found acceptable by DMEPA. There are no outstanding labeling issues.

12. Decision/Action/Risk Benefit Assessment

As the applicant has provided adequate CMC/Biopharmaceutics and Clinical Pharmacology information to support approval of the 5 mg 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), I recommend approval of this application.

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/s/

ERIC P BASTINGS
07/18/2014