CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204569Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	July 9, 2014
From	Ronald Farkas, MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 204569
Applicant	Merck
Date of Submission	February 14, 2014
PDUFA Goal Date	August 14, 2014
Proprietary Name / Established (USAN) names	Belsomra Established name: suvorexant
Dosage forms / Strength	5 mg, 10 mg, 15 mg, 20 mg
Proposed Indication(s)	Insomnia
Recommended:	Approval

1. Background

A Complete Response was issued on June 28, 2013 for the original New Drug Application for suvorexant. FDA concluded that substantial evidence of effectiveness for the treatment of insomnia had been demonstrated for suvorexant, but that because manufacturing data necessary to support approval of both a 5 mg and 10 mg dosage form not been submitted, the NDA could not be approved. On February 14, 2014, the sponsor submitted a Complete Response to address these deficiencies, containing chemistry, manufacturing and controls (CMC) information and two phase 1 bioavailability studies for the 5 mg and 10 mg tablets.

2. Review Findings

Updates to the drug substance section of the application were reviewed by the drug substance reviewer, Dr. Mohan Sapru. Dissolution was reviewed by the biopharmaceutics reviewer, Dr. Sandra Suarez. The drug product quality reviewer was Dr. Akm Khairuzzaman. Each of the above reviews found the submitted data acceptable and recommended approval. Dr. Khairuzzaman noted that the Office of Compliance made an overall recommendation as "acceptable" to all facilities related to this NDA.

The bioavailability studies were reviewed by the clinical pharmacology reviewer, Dr. Hristina Dimova. Study P055 evaluated the relative bioavailability between four 5 mg suvorexant tablets and one 20 mg suvorexant tablet. The pharmacokinetics of suvorexant following single-dose administration of four 5 mg tablets and one 20 mg tablet were similar, as assessed by AUC and Cmax. While not pre-specified, the 90% confidence interval of the geometric mean ratio (GMR) of these parameters was within the bioequivalence (BE) interval of 80.00-125.00%. Study P056 evaluated the relative bioavailability between two 10 mg suvorexant tablets and one 20 mg suvorexant tablet. The pharmacokinetics of suvorexant following single-dose administration of two 10 mg tablets and one 20 mg tablet were similar, as assessed by AUC and Cmax. While not

pre-specified, the 90% confidence interval of the GMR of these parameters was within the BE interval of 80.00-125.00%. The Clinical Pharmacology review concluded that the above findings were acceptable to support approval.

Patient labeling review of the Medication Guide was conducted by Twanda Scales, RN, MSN/Ed, and was found acceptable.

Nonclinical studies were also submitted by the sponsor in the Complete Response regarding retinal atrophy identified in the rat carcinogenicity study. The primary clinical reviewer for these studies was Dr. Richard Siarey. In two chronic toxicology studies in Sprague-Dawley and Long-Evans rats, suvorexant was found to increase the incidence of retinal atrophy, with the atrophy occurring later and at a lower incidence in the Long-Evans rats, suggesting that pigmentation may slow the development of retinal atrophy.

3. Conclusions

Approval is recommended.

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

/s/

RONALD H FARKAS
07/14/2014