CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204569Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service, Food and Drug Administration
Center for Drug Evaluation and Research

DATE: July 29, 2014

TO: File

THROUGH: Olen Stephens, Ph.D., Acting Branch Chief, ONDQA

FROM: Mohan K. Sapru, Ph.D., Senior CMC Reviewer

SUBJECT: Final Approval Recommendation from Chemistry, Manufacturing and Controls (CMC) for the Resubmitted NDA 204569 (Suvorexant).

Summary: The applicant, Merck Sharp & Dohme Corp., sought U.S. marketing approval for the NME NDA (Suvorexant Tablets) under the provisions of Section 505(b)(1). The initial NDA for suvorexant (MK-4305) tablets for the treatment of insomnia, submitted on August 30, 2012, proposed dosage strengths of 15 mg, 20 mg, 30 mg, and 40 mg. The NDA was recommended for approval from the CMC perspective. However, based on clinical considerations, the Agency issued a Complete Response (CR) letter on June 28, 2013, which included the requirement to revise the available strengths to 5 mg, 10 mg, 15 mg, and 20 mg. Based on CMC review of resubmitted NDA 204569, all the CMC issues have been resolved and the drug substance reviewer (refer to Dr. M. Sapru's memo, dated June 25, 2014) and drug product reviewer (refer to Dr. A. Khairuzzaman's memo, dated July 1, 2014) both have recommended approval.

Recommendation and Conclusion on Approvability: Given that Office of Compliance (OC) has issued an overall 'acceptable' recommendation for all the manufacturing facilities, including the (b) (4) manufacturing facility, from CMC perspective NDA 204569 is recommended for approval.

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/s/

MOHAN K SAPRU
07/29/2014

OLEN M STEPHENS
07/29/2014

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

/ tion:	NDA 204569/000	**Sponsor:**	MERCK SHARP DOHME
ι ode:	120		126 EAST LINCOLN AVE RY 33 208
Priority:	1		RAHWAY, NJ 070650900
Stamp Date:	30-AUG-2012	**Brand Name:**	SUVOREXANT
PDUFA Date:	14-AUG-2014	**Estab. Name:**	
Action Goal:		**Generic Name:**	
District Goal:	15-JUN-2014	**Product Number; Dosage Form; Ingredient; Strengths**	
		001; TABLET; SUVOREXANT; 15MG 002; TABLET; SUVOREXANT; 20MG 003; TABLET; SUVOREXANT; 30MG 004; TABLET; SUVOREXANT; 40MG	

FDA Contacts:	V. SHAH	Facility Reviewer	(HFD-320)	3017961750
	M. SAPRU	Prod Qual Reviewer		3017961718
	T. BOUIE	Product Quality PM		3017961649
	C. MICHALOSKI	Regulatory Project Mgr	(HFD-120)	3017961123
	M. HEIMANN	Team Leader		3017961678

Overall Recommendation:	ACCEPTABLE	on 28-JUL-2014	by T. SHARP	()	3017963208
	PENDING	on 26-FEB-2014	by EES_PROD		
	ACCEPTABLE	on 27-JUN-2013	by J. WILLIAMS	()	3017964196
	PENDING	on 12-SEP-2012	by EES_PROD		

.shment:	**CFN:** (b) (4)	**FEI:** (b) (4)	(b) (4)
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE PACKAGER		
Profile:	TABLETS, PROMPT RELEASE	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	21-SEP-2012		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

F ·hment:	**CFN:**	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	28-JUL-2014		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** 1036761	**FEI:** 1036761	
	MERCK SHARP & DOHME, WILSON FACILITY		
	WILSON, , UNITED STATES 278939613		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
M·· ·tone Date:	27-JUN-2013		
·n:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	MSD INTERNATIONAL GMBH (MSD IRELAND, BALLYDINE)		
	CLONMEL CO TIPPERARY, , IRELAND		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	29-MAY-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

F 'shment:	**CFN:** 2650155 **FEI:** 2650155		
	SCHERING-PLOUGH PRODUCTS, LLC		
	LAS PIEDRAS, , UNITED STATES 00771		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
Profile:	TABLETS, PROMPT RELEASE	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	15-MAY-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** **FEI:** (b) (4) (b) (4)		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	24-JUN-2013		
n:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

NDA 204-569

[redacted] (b) (4) (suvorexant) Tablets, 5 mg, 10 mg, 15 mg & 20 mg

Merck Sharp & Dohme Corp.

Akm Khairuzzaman, Ph.D.
Drug Product Quality Reviewer
ONDQA/DNDQA1/Branch 1

Reviewed for the Division of Neurology Products, HFD-120

Chemistry Review Data Sheet

1. NDA 204-569

2. REVIEW #: **2**

3. REVIEW DATE: 06/30/2014

4. DRUG PRODUCT QUALITY REVIEWER: Akm Khairuzzaman, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Resubmission	14-Feb-2014

7. NAME & ADDRESS OF APPLICANT:

Name	Merck Sharp & Dohme Corp.
Address	One Merck Drive P.O. Box 100 Whitehouse Station, NJ 08889
Representative	Nadine Margaretten, Ph.D.; Director, Worldwide Regulatory Affairs
Telephone	(732) 594-0373
FAX Number	N/A

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name	(b) (4)
Non-Proprietary Name (USAN)	Suvorexant
Code Names	L-001958419, MK-4305
Chemistry Type	1
Submission Priority	S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: For Treatment of Insomnia

11. DOSAGE FORM: Immediate Release Tablets

12. STRENGTH/POTENCY: 5 mg, 10 mg, 15 mg & 20 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __**X**__Rx _____OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

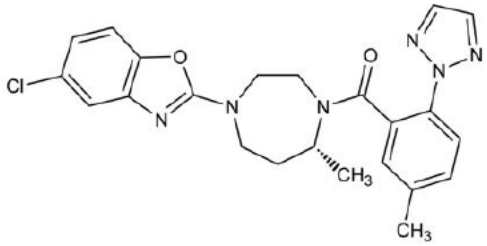
_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Names:
[(7*R*)-4-(5-Chloro-2-benzoxazolyl)hexahydro-7- methyl-1*H*-1,4-diazepin-1-yl][5-methyl-2-(2*H*-1,2,3-triazol-2- yl)phenyl] methanone

US Adopted Name (USAN): Suvorexant
Laboratory Codes: L-001958419, MK-4305
Chemical structures:



Chemical Formula: $C_{23}H_{23}ClN_6O_2$
Molecular Weight: 450.921

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: See Original CMC review Conducted by Dr. Akm Khairuzzaman

B. Other Documents:

N/A

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	27th June, 2013	
LNC	N/A	----	----
OSE-DMEPA		----	----
EA	Categorical Exclusion: Acceptable	See Review Date Above	A. Khairuzzaman, Ph.D.
Biopharmaceutics	Acceptable	06/23/2014	Sandra Suarez, Ph.D.
API	Acceptable	06/25/2014	Sapru Mohan, Ph.D.

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application (resubmitted) **is recommended** for approval from CMC perspective. Currently there are no pending issues related to drug product quality. On 27th June, 2013, the Office of Compliance (OC) has made an overall recommendation as "Acceptable" to all facilities related to this NDA.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no Phase 4 commitments.

II. Summary of Product Quality Assessments

During the first NDA review cycle, the agency recommended a Compete Response (dated 6/28/2013) due to clinical reason and recommended the applicant to develop lower strengths. As a result the applicant has withdrawn the higher strengths: 30 and 40 mg tablets and has resubmitted this NDA on 02/14/2014 along with two new lower strengths: 5 mg and 10 mg tablets besides previously reviewed 15 mg and 20 mg strength tablets. The applicant has provided some minor update on the drug substance section which is reviewed by the respective drug substance reviewer, Dr. Mohan Sapru. Regarding the drug product, it is to be noted that these two lower strengths (5 mg and 10 mg) are manufactured (b) (4) , the quality of which was acceptable during the first review cycle. The additional two lower strengths are (b) (4) reviewed in the first cycle. Therefore, there is not much CMC information in this resubmission that needs to be reviewed. However, due to introduction of these two new strengths, the applicant has updated many respective sections in the CMC part to reflect the addition of these two new strengths. The most important update to note here is the updated drug product specification that accommodated these two new strengths. The same tests and limits are applied to these new two strengths and therefore no further review on their respective analytical methods are necessary. Based on additional manufacturing experience, the applicant has introduced some additional changes to the process (b) (4) This will be further confirmed during process performance qualification (b) (4) These changes is not expected to alter the product quality attributes since they were extensively reviewed in the first cycle and considered as low risk. This resubmission also includes updated and executed batch records for these two new lower strengths which were found to be acceptable by this reviewer. The dissolution limit proposed is the same for the

other strength and will be reviewed by the respective ONDQA biopharmaceutics reviewer Dr. Sandra Suarez.

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In the first submission up to 52 weeks (13 months) of formal stability data were submitted from three FSS (primary stability) batches of each of the 15 mg, 30 mg, and 40 mg strength using the final market composition in commercial packaging (aluminum/aluminum blister Package). Based on the review of these data, the reviewer was in agreement with the applicant's proposed shelf life (b) (4) It is to be noted that (b) (4) was not tested. This resubmission includes additional data (up to 104 weeks) for these higher strengths. These additional data do not show any further changes in quality attributes and therefore there **the proposed shelf life of 36 months for 15 mg and 20 mg tablets can be granted**. For the two new strengths (5 mg and 10 mg), up to 6 months of data from the long term and accelerated conditions were submitted. These data do not show any trend from any quality attributes of the product. Although the stability data is limited for these two new strengths, based on similarities of formulation, process, container closure, and (b) (4) strategy, it is expected that the 5 mg and 10 mg tablets will behave the same on stability as the higher (b) (4) strengths from both physical and chemical perspectives. Therefore, a **shelf life of 12 months for 5 mg and 10 mg tablets can be granted as per ICH Q1E**.

There are no pending drug product related deficiencies for this NDA. Therefore, this NDA **can be recommended** for approval from Product Quality Perspective.

III. Administrative

A. Reviewer's Signature

/s/ A. Khairuzzaman, Ph.D.

B. Endorsement Block

Drug Product Quality Reviewer:	Akm Khairuzzaman, Ph.D.
Pharmaceutical Assessment Lead:	Martha Heimann, Ph.D.
Branch Chief:	Olen Stephens, Ph.D.
Project Manager:	Teshara Bouie

C. CC Block

Orig. NDA 204-569
HFD-120/Division File

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/s/

AKM KHAIRUZZAMAN
06/30/2014
Recommended for approval from CMC point of view

OLEN M STEPHENS
07/01/2014

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service, Food and Drug Administration
Center for Drug Evaluation and Research

DATE: June 25, 2014

TO: File

THROUGH: Olen Stephens, Ph.D., Acting Branch Chief, ONDQA

FROM: Mohan K. Sapru, Ph.D., Senior CMC Reviewer

SUBJECT: ***Chemistry, Manufacturing and Controls (CMC) Review Update for the Drug Substance Concerning the NDA 204569 (Suvorexant) Resubmission***

Background: The applicant, Merck Sharp & Dohme Corp., sought U.S. marketing approval for the NME NDA (Suvorexant Tablets) under the provisions of Section 505(b)(1). The applicant's development of the commercial manufacturing process for drug substance and drug product has followed risk-based, quality-by-design (QbD) approach. The initial NDA for suvorexant (MK-4305) tablets for the treatment of insomnia, submitted August 30, 2012, proposed dosage strengths of 15 mg, 20 mg, 30 mg, and 40 mg. The NDA was recommended for approval from the CMC perspective. However, based on clinical considerations, the Agency issued a Complete Response (CR) letter on June 28, 2013, which included the requirement to revise the available strengths to 5 mg, 10 mg, 15 mg, and 20 mg.

Summary of Drug Substance-Related Updates: In the drug substance sections (Module 3), minor updates to analytical methods and acceptance criteria to starting materials and a raw material have been included in the resubmission. In addition, (b) (4) has been added as a manufacturer of the (b) (4) intermediate. Batch analyses data for this intermediate from the new supplier have been included along with historical data from the current supplier. Batch analyses data have also been provided for suvorexant drug substance that was manufactured (b) (4) Additional drug substance stability data are provided to support a (b) (4) re-test date. The details concerning the resubmission updates and their evaluations are listed below.

Section	Proposed Change/Update
S.2.1	❖ **Manufacturer:** (b) (4) has been added as a manufacturer of the (b) (4) intermediate. Specifically, manufacture, packaging and release testing of (b) (4) intermediate will be carried out at the following facility: (b) (4)

Reviewer Evaluation:

❖ *The overall recommendation from the Office of Compliance (OC) for the* (b) (4) *manufacturing facility is still awaited.*

Section	*Proposed Change/Update*
S.2.3.	• **Control of Materials**: The acceptance criteria for the unspecified impurities (b) (4) have been revised to align it with the acceptance criteria that were in place during original process validation activities. • The acceptance criterion for residual (b) (4) has been revised (b) (4) • The (b) (4) impurities method for (b) (4) starting material has been replaced with a gas chromatography (GC) method. Chromatographic conditions: (b) (4) • The acceptance criterion (b) (4) has been updated to include quantification of residual (b) (4) by area%.
S.2.6.	• Starting material and intermediate designations have been updated to align with the changes implemented previously upon Agency review. • A discussion on the (b) (4) manufacturing process development has been included. • The justification to maintain (or revise) some open-ended process parameter ranges, provided previously during the Agency review (Merck Responses to Question), has been included.
S.3.2.	• (b) (4) are presented as starting materials and (b) (4) as an intermediate (as agreed to during Agency review).

Reviewer Evaluation: Adequate.

❖ *The applicant has proposed to revise the acceptance limit for any unspecified impurity in the starting material (b) (4) from a maximum of (b) (4) area% to a maximum of (b) (4) area%. This proposed change is acceptable, mainly, because it does not have any meaningful impact on the drug substance quality control strategy (b) (4)*

❖ *Regarding the acceptance criteria for (b) (4) a potentially genotoxic impurity in the starting material (b) (4) the Agency had previously recommended that its residual levels in the staring material be controlled within the Threshold of Toxicological Concern (TTC) limit (b) (4) Because the suvorexant maximum daily dose in the resubmission has been revised from 40 mg to 20 mg, the acceptance limit (b) (4) has been appropriately updated from TTC limit (b) (4)*

- *The (b) (4) impurities method (b) (4) was suitable for its intended use at the time of the initial filing. However, based on Agency recommendation, there was a change in designation of this material (b) (4) to GMP starting material. The applicant has replaced the (b) (4) method with a GC method. The GC method offers improved detection and quantification of impurities and has been appropriately validated.*

- *The unit of measure used to quantify residual (b) (4) content (b) (4) has been revised (b) (4) to (b) (4) area%. A correlation (b) (4) has been established (b) (4)*

- *The changes listed in S.2.6. and S.3.2 have been previously agreed upon by the applicant in compliance with the Agency recommendations.*

Section	Proposed Change/Update
S.4.4.	• Batch analysis data are provided for commercial batches (b) (4) manufactured (b) (4) • Historical data from the previously registered supplier (b) (4) is provided for comparison with material manufactured (b) (4) • Batch analysis data are provided for suvorexant drug substance manufactured (b) (4) • Residual heavy metals have been added to the commercial batches provided in the original NDA, and for the new commercial batches. • The previous commitment (during review of the original NDA) by the sponsor to implement a heavy metals specification is described. • The maximum daily dose of suvorexant has been updated from 40 mg to 20 mg
S.4.5.	• Expanded the list of those batches which used (b) (4) in the manufacturing process to include the new commercial batches described in S.4.4.
S.7.1.	• The re-test period of suvorexant drug substance has been updated (b) (4)
S.7.3.	• Additional stability data are provided for three stability batches (18 and 24-month time points) to support the updated re-test period (b) (4)

S.4.4., S.4.5: Batch Analysis Data and Justification of Specification:

The applicant has provided additional batch analyses data, including data for the commercial lots BTA-404, -405 and -406 (Table 4) which have been manufactured with (b) (4) intermediate supplied (b) (4) The manufacturing process used (b) (4) is the same process originally developed by the applicant and previously executed (b) (4) As further evidence to the equivalency of the (b) (4) intermediate from both vendors, batch analyses data from the validation campaigns from each vendor are provided in Table 5.

Table 4: Batch Analysis Results for Suvorexant Commercial Lot Nos. BTA-404 to BTA-406

Lot Number Batch ID	BTA-404	BTA-405	BTA-406
Site of Manufacture Date of Manufacture Batch Size	(b) (4)		
Process No.	Commercial	Commercial	Commercial
Test			
Appearance§	Conforms	Conforms	Conforms
Assay (w/w%)†	(b) (4)		
(b) (4)			
Identity by IR‡	Conforms	Conforms	Conforms
Impurities (area %)			
(b) (4)	N.D.	N.D.	N.D.
	N.D.	N.D.	N.D.
Any Unspecified Impurity	N.D.	N.D.	N.D.
Total Impurities	N.D.	N.D.	N.D.
Residual Solvents (w/w%)	(b) (4)		
(b) (4)			
Heavy Metals (ppm)			

N.D. = Not Detected
† Calculated on (b) (4) basis
‡ Conforms is equivalent to conforming to the reference sample
§ Conforms is equivalent to clean, white to off-white powder

Table 5: Batch Analysis Results (b) (4) **Manufactured** (b) (4)

(b) (4)

Reviewer Evaluation: Adequate.

- *The applicant's above-listed updates in S.4.4., S.4.5 are acceptable. Specifically, the drug substance batches BTA-404, BTA-405 and BTA-406 (Table 4), which have been manufactured*

with (b) (4) *intermediate supplied* (b) (4) *meet the specification criteria and are suitable for the intended use.*

- *The batch analysis data provided in Table 5 point to the equivalency of the* (b) (4) *intermediate supplied by the previous vendor* (b) (4) *and the current vendor* (b) (4)

- *Regarding drug specification (S.4.5), in most cases the acceptance criteria have been derived from statistically designed multi-factor experimental studies using Quality by Design principles (QbD), including assessment of data and the potential impact to the suvorexant manufacturing process. In compliance with the Agency recommendation, the applicant has included specification for heavy metals content in the drug substance. The levels of USP heavy metals have been evaluated using an Inductively Coupled Plasma Mass Spectroscopy (ICP-MS) method. All commercial scale lots have been tested using the USP (<231>) procedure II for heavy metals, and found to contain* (b) (4) *heavy metals. These data support a heavy metals acceptance criterion of not-more-than (NMT)* (b) (4) *for suvorexant drug substance.*

S.7.1., S.7.3: Representative Updated Stability Data (25°C/60% RH):

MANUFACTURING SITE	BATCH SIZE
Rahway, NJ, USA	(b) (4)
DATE MANUFACTURED	**CONTAINER DESCRIPTION**
01-Oct-2008	(b) (4)

(b) (4)

Reviewer Evaluation: Adequate.

- *The applicant has demonstrated 36-month stability under long-term storage conditions of 25°C/60%RH. None of the monitored drug substance attributes have shown trend of any significant changes during the storage period of 36 months. The stability data provided in the resubmitted NDA support the updated re-test period* (b) (4)

Recommendation and Conclusion on Approvability: From the perspective of CMC review of the suvorexant drug substance, the resubmitted new drug application (NDA 204569) is recommended for approval provided the Office of Compliance (OC) issues an overall 'acceptable' recommendation for the (b) (4) manufacturing facility.

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/s/

MOHAN K SAPRU
06/25/2014

OLEN M STEPHENS
06/25/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION REPORT SUMMARY

TO: Akm Khairuzzaman, CMC Reviewer
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: Akm.Khairuzzaman@fda.hhs.gov
Phone: (301)-796-3886
Fax: (301)-796-9747

FROM: FDA
Division of Pharmaceutical Analysis
Michael Trehy, MVP Coordinator
Suite 1002
1114 Market Street
St. Louis, MO 63101
Phone: (314) 539-3815

Through: John Kauffman, Acting Deputy Director
Phone: (314) 539-2168

SUBJECT: Methods Validation Report Summary

Application Number: 204569

Name of Product: (b) (4) (suvorexant) Tablets

Applicant: Merck

Applicant's Contact Person: Nadine Margaretten

Address: 126 Lincoln Avenue, P.O. Box 2000, RY33-208, Rahway, NJ 07065

Telephone: (732) 594-0373 Fax: (732) 594-5235

Date Methods Validation Consult Request Form Received by DPA: 11/19/12

Date Methods Validation Package Received by DPA: 11/19/12

Date Samples Received by DPA: 12/10/12

Date Analytical Completed by DPA: 5/10/13

Laboratory Classification: **1.** Methods are acceptable for control and regulatory purposes. ☒
2. Methods are acceptable with modifications (as stated in accompanying report). ☐
3. Methods are unacceptable for regulatory purposes. ☐

Comments: See attached summary report for comments and sample results.

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
St. Louis, MO 63101
Tel. (314) 539-3797

Date: May 13, 2013

To: Martha R. Heimann, Ph.D. and Akm Khairuzzaman, Ph.D. Office of New Drug Quality Assessment

Through: John Kauffman, Acting Deputy Director, Division of Pharmaceutical Analysis

From: Kallol Biswas, Ph.D., Chemist

Subject: Method Validation for NDA 204569 (b) (4) (suvorexant) Tablets

The following methods were evaluated and are acceptable for quality control and regulatory purposes:

Suvorexant Tablets: Assay, Degradates, and Identity- HPLC Method Number: A3691M02.000

Suvorexant : Assay and Impurities- HPLC Method Number: A2001M01.001

Link to analysts work sheets at http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f8804501ca

Results Summary

Method	Results
Suvorexant Tablets: Assay, Degradates, and Identity- HPLC Method Number: A3691M02.000	**Assay results** Prep 1 (b) (4) Prep 2 Average Specification: (b) (4) of Label Claim Meets Specification

No degradants greater than (b) (4) were found in the tablet sample solutions.

Method	Results
Suvorexant : Assay and Impurities- HPLC Method Number: A2001M01.001	Assay Results Prep 1 (b) (4) Prep 2 **Average** Specification : (b) (4) Meets specification

No impurities greater than (b) (4) were found in the drug substance sample solutions.

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/s/

MICHAEL L TREHY
05/14/2013

JOHN F KAUFFMAN
05/14/2013

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 28, 2013

TO: File

THROUGH: Ramesh K. Sood, Ph.D., Branch Chief, ONDQA

FROM: Mohan K. Sapru, Ph.D., CMC Reviewer for Drug Substance
Akm Khairuzzaman, Ph.D., CMC Reviewer for Drug Product

SUBJECT: Final CMC Approval Recommendation for NDA 204-569 (Suvorexant)

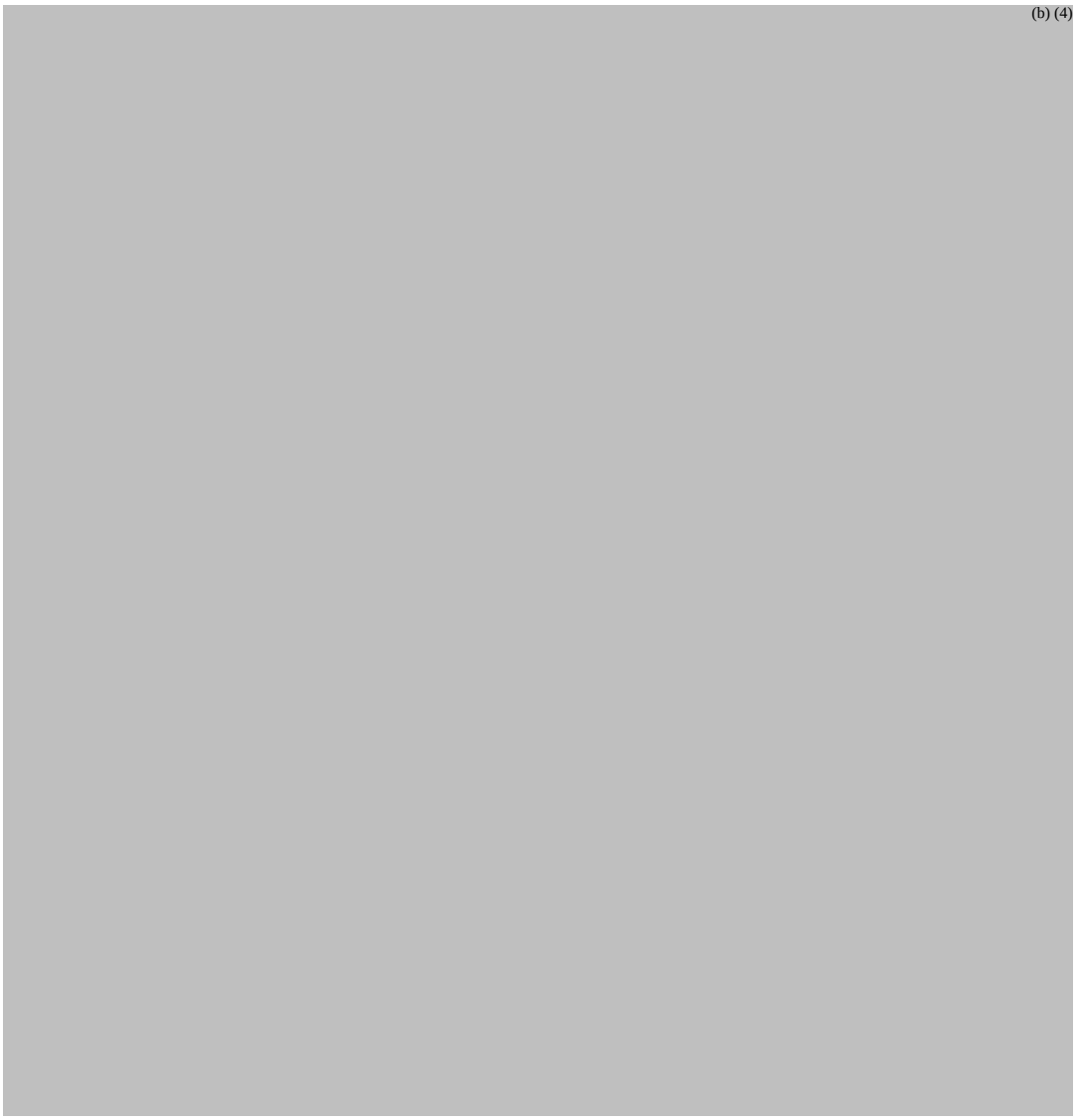
The applicant, Merck Sharp & Dohme Corp., sought U.S. marketing approval for Suvorexant under the provisions of Section 505(b)(1). The applicant's development of the commercial manufacturing process for suvorexant drug substance and drug product has followed risk-based, Quality-by-Design (QbD) approach {for details refer to drug substance review by Dr. Mohan K Sapru (dated 04-29-2013), and b) drug product review by Dr. Akm Khairuzzaman, dated 04-30-2013}. Based on drug substance review, the applicant was recommended to include a test and an appropriate acceptance criterion for (b) (4) a potentially genotoxic impurity, in the specification for either the starting material (b) (4) or the drug substance, and provide details of analytical procedure used to measure residual levels of this impurity. Alternatively, the applicant was given the option to demonstrate that (b) (4) is negative in an in vitro bacterial reverse mutation (Ames) assay.

In response, the applicant agreed to the Agency recommendation and included a test (b) (4) with an acceptance criterion of maximum (b) (4) (the TTC) for the starting material (b) (4) The acceptance limit (b) (4) and the revised analytical procedure details are summarized below:

Items	Tests and Expected Values
	(b) (4)

In conclusion, the applicant's response is adequate and the genotoxic impurity issue is considered resolved. On 27th June, 2013, the Office of Compliance (OC) has made an overall recommendation as "Acceptable" to all facilities related to this NDA. Therefore, from Chemistry, Manufacturing and Control (CMC) point of view, this NDA is recommended for approval.

ATTACHMENT
EES Overal Recommendation



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/s/

MOHAN K SAPRU
06/28/2013

RAMESH K SOOD
06/28/2013

[redacted] (Suvorexant) Tablets

NDA 204-569

Summary Basis for Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: Merck Sharp & Dohme Corp.,
P.O. Box. 100
Whitehouse Station, NJ 08889

Indication: For the treatment of insomnia.

Presentation: The product is in four different strengths; 15 mg, 20 mg, 30 mg and 40 mg. The different strength tablets are differentiated by color, shape and strength identifier numbers on one side of the tablets. The tablets will be packaged unit-of-use in [redacted] blisters [redacted] with aluminum film.

EER Status: Overall recommendation is pending as of 24-June-2013.

Consults: ONDQA Biopharmaceutics – Acceptable as per Dr. Sandra Suarez Sharp's review dated 30-Apr-13.
Methods Validation – The methods sent to FDA labs were found to be acceptable for quality control and regulatory purposes (14-May-2013).
EA – Categorical exclusion granted under 21 CFR §25.31(c)

Post-Approval Agreements: None

Drug Substance:

The drug substance, surovexant, is a new molecular entity and is the first in orexin receptor reversible antagonist class. The drug substance is a white to off-white powder and practically insoluble in water. The compound has one chiral center (b) (4) The drug substance manufacturing process is designed (b) (4) The drug substance manufacturing process is a multi-step chemical process. The applicant demonstrated a good understanding of the manufacturing process obtained through enhanced experimentation using quality by design principles. Additionally, the drug substance quality is ensured through appropriate in-process controls throughout the manufacturing process and the appropriate final drug substance specification. The drug substance release specification includes tests and acceptance criteria for drug substance critical quality attributes, e.g., description, identification, purity, residual levels of impurities, residual solvents and residual metal. The analytical procedures have been adequately described and validated to control the quality of the drug substance. The stability of the drug substance has been demonstrated through appropriate stability studies to support a retest period (b) (4)

Drug product:

The manufacturing process for surovexant tablets is divided (b) (4) Additionally, the drug product final specification ensures that the drug product of acceptable quality is manufactured consistently using the proposed process. The drug product specification includes tests and acceptance criteria for appearance, identity, assay, degradants, dissolution, dose uniformity and (b) (4). The analytical procedures for the drug product are adequately described and validated. The provided stability data support a (b) (4) expiration period for this product.

The drug product is stored at 20°C-25°C (68-77°F). Excursions permitted 15-30ºC (59-86ºF).

Conclusion: Adequate from CMC perspective.

Additional Items:

All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

Overall Conclusion: "Approval" pending "acceptable" recommendation from OC.

All the CMC related issues have been resolved. The final recommendation from the Office of Compliance is pending at the time of writing this memorandum. A final memorandum with CMC recommendation will be entered into DARRTS once a recommendation from the OC is received.

Ramesh K. Sood, Ph.D.
Acting Director, DPA I/ONDQA

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/s/

RAMESH K SOOD
06/24/2013

CMC Memo to File

To:	NDA-204569
Date	24 June 2013
Sponsor:	Merck Sharp & Dohme Corp
Drug:	Suvorexant
Subject	CMC Amendments & Recommendation
Reviewer	Dr. Akm Khairuzzaman

On 06/21/13 and 05/31/13, Merck Sharp & Dohme Corp has submitted CMC amendments for reinstating the original content uniformity limit (which is based on USP <905>) in specification and keeping the CDER Compliance Reviewer's recommended tighter limit (during the pre-approval inspection) as an internal alert. This proposal was based on a teleconference dated 06/19/2013, which was attended by the ONDQA, Office of Compliance and Merck representatives. The CMC amendment also reported (b) (4) [redacted] The reviewer is in agreement with the company's strategy (b) (4) [redacted]

These recent amendments do not change the original recommendation "Not Recommended for Approval from CMC point of view" since the Office of Compliance (OC) overall recommendation is still pending. All CMC issues have been resolved at this stage except the final recommendation from the OC. A final memorandum with CMC approvability recommendation will be entered in DARRTS after the recommendation from OC.

HFD-/Division File
HFD-120

Akm Khairuzzaman, Ph.D.
Chemistry Reviewer

Martha Heimann, Ph.D.
CMC Lead, ONDQA

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/s/

AKM KHAIRUZZAMAN
06/24/2013
CMC Approval is Pending for Office of Compliance Overall Recommendation on Facilities

RAMESH K SOOD
06/24/2013

NDA 204-569

[redacted] (b) (4) (suvorexant) Tablets, 15 mg, 20 mg, 30 mg & 40 mg

Merck Sharp & Dohme Corp.

Akm Khairuzzaman, Ph.D.
Drug Product Quality Reviewer
ONDQA/DNDQA1/Branch 1

Reviewed for the Division of Neurology Products, HFD-120

Table of Contents

Chemistry Review Data Sheet

1. NDA 204-569

2. REVIEW #: 1

3. REVIEW DATE: 04/29/2013

4. DRUG PRODUCT QUALITY REVIEWER: Akm Khairuzzaman, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	29-August-2012
CMC amendment (74 day letter comment response)	12-December-2012
CMC amendment	11-March-2013
CMC amendment (74 day letter comment response)	29-March-2013
CMC Amendment	April 29, 2013

7. NAME & ADDRESS OF APPLICANT:

Name	Merck Sharp & Dohme Corp.
Address	One Merck Drive P.O. Box 100 Whitehouse Station, NJ 08889
Representative	Nadine Margaretten, Ph.D.; Director, Worldwide Regulatory Affairs
Telephone	(732) 594-0373
FAX Number	N/A

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name	(b) (4)
Non-Proprietary Name (USAN)	Suvorexant
Code Names	L-001958419, MK-4305
Chemistry Type	1
Submission Priority	S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: For Treatment of Insomnia

11. DOSAGE FORM: Immediate Release Tablets

12. STRENGTH/POTENCY: 15 mg, 20 mg, 30 mg & 40 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __**X**__Rx _____OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

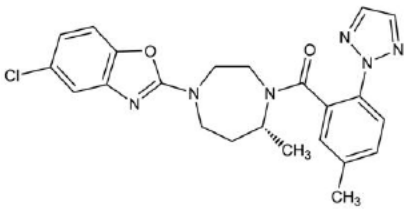
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Names:
[(7*R*)-4-(5-Chloro-2-benzoxazolyl)hexahydro-7- methyl-1*H*-1,4-diazepin-1-yl][5-methyl-2-(2*H*-1,2,3-triazol-2- yl)phenyl]methanone

US Adopted Name (USAN): Suvorexant
Laboratory Codes: L-001958419, MK-4305
Chemical structures:



Chemical Formula: $C_{23}H_{23}ClN_6O_2$
Molecular Weight: 450.921

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED
(b) (4)	III	(b) (4)		4	N/A	-
	III			4	N/A	-

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

N/A

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
LNC	N/A	----	----
Methods Validation	Necessary (Sent out to St. Louis FDA lab)		
OSE-DMEPA		----	----
EA	Categorical Exclusion: Acceptable	See Review Date Above	A. Khairuzzaman, Ph.D.
Biopharmaceutics	Not Given Yet	04/29/2013	Sandra Suarez, Ph.D.

The Chemistry Review for NDA 204-569

This review assesses the Drug Product aspects of the NDA. Drug Substance quality aspects are reviewed separately by Dr. Mohan Sapru.

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application **cannot be recommended** for approval from CMC perspective in its current form. This recommendation is for the drug product portion of the NDA. The final CMC recommendation for the NDA will be dependent on Dr. Mohan Sapru's review of the drug substance as well as the Office of Compliance (OC). Currently there are no pending issues related to drug product quality. However, the Office of Compliance (OC) has not yet given an overall acceptable recommendation for the manufacturing and testing facilities.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no Phase 4 commitments.

II. Summary of Product Quality Assessments

A. Description of the Drug Product

(b) (4) is an orexin receptor antagonist indicated for the treatment of insomnia. The active component in the drug product, suvorexant is a new molecular entity. The drug product is an immediate release film coated product with the Merck logo and strength identifying specific number on one side and plain on the other side. There are four proposed strengths for this product: 15 mg, 20 mg, 30 mg and 40 mg tablets. All strengths are dose proportional. The drug product was formulated using compendial excipient such as: polyvinylpyrrolidone/vinyl acetate copolymer, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate (b) (4) and (b) (4) coating component.

The molecule, suvorexant is lipophilic (log D ~ 3.73) and practically insoluble in water. Based on *in vivo* PK studies and the *in vitro* permeability (Caco-2 membrane permeability)

studies the molecule could be possibly a BCS class II compound, however no formal designation has been given by the agency's BCS committee. Since the compound is insoluble and the indication of the drug is insomnia, the challenge with the Applicant was to develop a product (b) (4)

The entire manufacturing process is divided (b) (4)

The applicant has utilized a quality by design approach to develop this drug product and has proposed design spaces for several unit operations. Use (b) (4) has been proposed for many of their manufacturing unit operations (b) (4)

A (b) (4) method is used (b) (4) The method was found to be acceptable by this reviewer for monitoring these in process controls.

The applicant has proposed design spaces for most of the unit operations for drug product manufacture. (b) (4)

(b) (4)

.

Appropriate drug product specification is in place which includes: appearance, identity (HPLC and UV), assay, degradates, dissolution, dose uniformity (b) (4) No specific tests for measuring the (b) (4) content in the drug product. It is acceptable by the reviewer only if the drug product is manufactured (b) (4)

The analytical methods to be used for the release and stability of the finished products are primarily HPLC and UV method, both found to be adequate based on the method validation data. Other analytical methods (b) (4) were also found to be adequate by this reviewer.

Up to 52 weeks (13 months) of formal stability data were submitted which were generated from three FSS (primary stability) batches of each of the 15 mg, 30 mg, and 40 mg strength using the final market composition in commercial packaging (aluminum/aluminum blister Package). (b) (4) Additionally, one batch each strength from the (1) commercial manufacturing site (Puerto Rico) at full commercial scale were also provided along with 39 weeks (~10 months) of long term condition data and 26 weeks of accelerated condition data were provided to the agency. Stability parameters tested were: assay, appearance, impurities, hardness, thickness, disintegration, dissolution and (b) (4) drug content. The 12 months long terms (25°C/60%RH) stability data and the 6 months accelerated (40°C/75%RH) stability data show that the drug product is chemically very stable and no sign of any trend in any of the stability parameters were observed by this reviewer. Most importantly, there was no sign (b) (4) when they are re-evaluated recently (b) (4)

Therefore, it is recommended to store tablets in the original package until use. Applicant has proposed for a (b) (4) product shelf life based on these data. In absence of any trend in any stability parameter, and more importantly in absence of any sign (b) (4) this reviewer is in agreement that the product shelf life (b) (4) can be granted.

The Applicant has satisfactorily responded on all drug product related on 11th and 29th March, 2013 and April 29th, 2013 to all the CMC deficiencies. There are no pending drug product related deficiencies for this NDA. However, the Office of Compliance has not yet

given an overall acceptance for the manufacturing facility and therefore, this NDA **cannot be recommended** for approval from Product Quality Perspective.

B. Description of How the Drug Product is Intended to be Used

(b) (4) (suvorexant) Tablets are for oral administration for the treatment of insomnia. The product is in four different strengths: 15 mg, 20 mg, 30 mg and 40 mg. The recommended dose is 40 mg once daily. A lower dose of 20 mg once daily may be appropriate for some patients based on individual tolerability. The dose should not exceed 40 mg per day. The tablet may be taken with or without food and immediately before bedtime.

C. Basis for Approvability or Not-Approval Recommendation

This new drug application **cannot** be recommended for approval from the perspective of chemistry, manufacturing and controls because the Office of Compliance has not yet given an overall acceptance for the manufacturing facility.

III. Administrative

A. Reviewer's Signature

/s/ A. Khairuzzaman, Ph.D.

B. Endorsement Block

Drug Product Quality Reviewer:	Akm Khairuzzaman, Ph.D.
Pharmaceutical Assessment Lead:	Martha Heimann, Ph.D.
Branch Chief:	Ramesh Sood, Ph.D.
Project Manager:	Teshara Bouie

C. CC Block

Orig. NDA 204-569
HFD-120/Division File

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/s/

AKM KHAIRUZZAMAN

04/29/2013

This NDA is not recommended for approval from the perspective of chemistry, manufacturing and controls.

RAMESH K SOOD

04/30/2013

NDA 204-569 (Suvorexant)
(QbD-Based NME NDA)

Merck Sharp & Dohme Corp.

Drug Substance Review

Mohan K. Sapru, Ph.D.
Office of New Drug Quality Assessment
Pre-Marketing Assessment Division I/Branch I

Reviewed for the Division of Neurology Products, HFD-120

Table of Contents

Chemistry Review Data Sheet

1. NDA: 204-569

2. REVIEW #: 1

3. REVIEW COMPLETION DATE: 09-April-2013

4. REVIEWER: Mohan K. Sapru, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	N/A

6. SUBMISSION(S) REVIEWED:

Submission (s) Reviewed	Document Date
Original Submission	30-August-2012
CMC Amendment (74-Day Comment Response)	12-December-2012
CMC Amendment (Mid-Cycle Review Deficiency Response	11-March-2013
CMC Amendment (Deficiency Response	29-March-2013

7. NAME & ADDRESS OF APPLICANT:

Name and Address: Merck Sharp & Dohme Corp.
One Merck Drive, P.O Box 100
Whitehouse Station, NJ 08889.

Telephone: 732-594-0373

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proposed Proprietary Name: (b) (4)

b) Non-Proprietary Name (USAN): Suvorexant

c) Code Name MK-4305

d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: The application was submitted under Section 505(b)(1) of the Federal Food Drug and Cosmetic Act and 21 CFR §314.50.

10. PHARMACOL. CATEGORY/INDICATION: Reversible antagonist for orexin receptors (OX_1R and OX_2R) aimed to inhibit activation of wakefulness-promoting neurons of the arousal system for the treatment of insomnia.

11. DOSAGE FORM: Immediate-release tablets.

12. STRENGTH/POTENCY: 15 mg, 20 mg, 30 mg, and 40 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS Product – Form Completed.

___X_Not a SPOTS Product.

16. CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT, STRUCTURAL FORMULA:

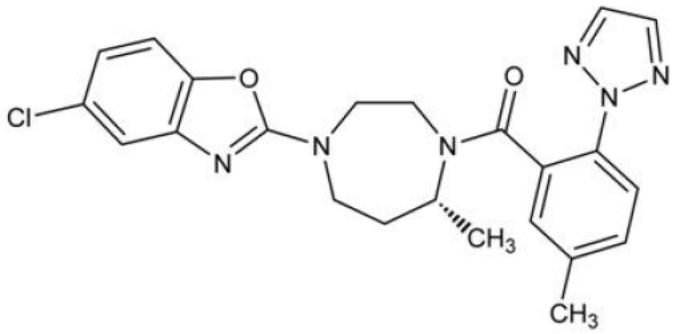
Chemistry Review Data Sheet

Chemical Name: [(7*R*)-4-(5-Chloro-1,3-benzoxazol-2-yl)-7-methyl-1,4-diazepan-1-yl][5-methyl-2-(2*H*-1,2,3-triazol-2- yl)phenyl]methanone.

Molecular Formula: $C_{23}H_{23}ClN_6O_2$

Molecular Weight: 450.92

Structure:



17. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
Methods Validation	Consult sent for internal validation to the FDA St. Louis Lab.	09-April-2013	
Environmental Assessment	Categorical Exclusion	09-April-2013	Mohan K. Sapru, Ph.D.

The Executive Summary (NDA 204569)

I. Recommendations.

A. Recommendation and Conclusion on Approvability.

From the chemistry, manufacturing and controls (CMC) perspective concerning the suvorexant drug substance, this new drug application (NDA 204569) will not be recommended for approval unless a) the applicant satisfactorily addresses the pending CMC deficiency concerning the control of a potential genotoxic impurity, and b) Office of Compliance issues an overall acceptable recommendation for all the relevant manufacturing and testing facilities. A follow up memorandum, which specifies the final CMC recommendation, will be submitted after the above-specified deficiencies are satisfactorily resolved. For recommendation regarding the suvorexant drug product, refer to the CMC review by Dr. Akm Khairuzzaman.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.

Not applicable at this stage.

II. Summary of Chemistry Assessments.

Description of the Drug Substance.

The drug substance suvorexant, a new molecular entity (NME), is the first in class orexin receptor reversible antagonist proposed for the treatment of patients with insomnia. The drug substance, a white to off-white powder, is practically insoluble in water and has been classified as BCS Class II compound. Suvorexant has been formulated for oral administration as an immediate-release tablet (15 mg, 20 mg, 30 mg, and 40 mg). Using ultraviolet (UV), infrared (IR) spectroscopy, ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy, [redacted] (b) (4) and mass spectroscopy, the applicant has adequately characterized the drug substance. Suvorexant has one chiral center, and its enantiomeric purity is controlled by chiral HPLC [redacted] (b) (4)

The applicant's development of the commercial manufacturing process for suvorexant drug substance has followed risk-based, Quality-by-Design (QbD) approach. The applicant's QbD-based approach has included a) identification of the critical quality attributes (CQA) and quality target products (QTTPs) based on risk assessment and developmental studies, b) defining of design space ranges through both statistically designed multifactor and supplementary

conventional experiments, c) execution of statistically designed multifactor experiments for key operations pivotal to impurity generation or rejection, d) execution of traditional experiments for process parameters influencing drug substance CQAs through straightforward, univariate routes that are understood to have no meaningful interaction with other process inputs, e) defining of proven acceptable ranges via true one factor-at-a-time experiments for some peripheral process parameters with limited roles in impurity generation/rejection (b) (4) and f) confirmation of design space ranges with worst-case-scenario experiments or fate/purge evaluations. Specifically, the applicant has employed design of experiments (DOEs)-based studies to understand the interaction of the material attributes and critical process parameters.

The drug substance manufacturing process is a multi-step chemical process. The details of risk assessment and design of experiments (DOEs), including experimental data used to define design space ranges for critical manufacturing steps, have been appropriately provided and are acceptable. The applicant has defined the proposed design space as the multifactor space over which acceptable product quality has been demonstrated or can be inferred from engineering or scientific first principles. Experimental evidence demonstrates that (b) (4) is generated reproducibly and robustly within the proposed design space. The applicant has sought regulatory flexibility for movement within the proposed design space ranges. Deviations outside the prescribed ranges will trigger investigations consistent with manufacturing site Quality Systems.

The drug substance quality is controlled through a well-defined control strategy, which includes raw materials specifications (material attributes), appropriate in-process testing, and release specification. The specification for suvorexant drug substance has been established in view of enhanced understanding of the process via QbD approach, analysis of stability results and batch release data for lots used in toxicological and safety assessment studies. Specifically, the release specification includes tests and appropriate acceptance criteria for drug substance CQAs such as description, identification, purity, residual levels of impurities, including chiral impurity, residual solvents and heavy metals. All the non-compendial analytical methods have been validated for critical analytical parameters such as linearity, specificity, precision, accuracy, solution stability, and robustness, and are suitable for intended applications. Regarding control strategies, including establishing of drug substance release specification, it is critical to correlate drug substance quality attributes to drug product quality attributes. In view of this it is important to note that the suvorexant drug product is formulated (b) (4)

Consequently, several of the physical properties of the drug substance (b) (4) are unlikely to translate to any meaningful effect on the critical quality attributes of the drug product.

The container/closure system used for the packaging of suvorexant drug substance for long-term storage (b) (4) providing equivalent or enhanced protection. Stability data show that there are no significant changes in the description, assay, impurity levels, water content, chiral purity, (b) (4) following storage of the drug substance under long-term conditions of 25°C/60%RH, or under accelerated conditions of 40ºC/75% RH for a period of up to 36 months and 6 months, respectively. No special consideration for protection from light is

indicated [redacted] in photostability studies. Regarding post-marketing commitment, the applicant has committed that three commitment commercial validation batches will be tested for stability under long-term and accelerated conditions

Description of the Drug Product: See the drug product review by Dr. Akm Khairuzzaman.

C. Basis for Approvability or Not-Approval Recommendation.

Based on the review of the original submission, several drug substance-specific deficiencies were identified and communicated to the applicant via 74-day Information Request (IR) and mid-cycle review Deficiency Letter. These deficiencies mainly concerned inadequate information and/or data regarding DOEs (input/output data, multivariate combinations used and the statistical analysis), commercial manufacturing process description, scale-up verification of the design of space, open design space/proven acceptable ranges, impurity fate/purge studies, risk-based rationale for process parameter selection, [redacted] and control of potentially genotoxic impurities. In addition, the Agency disagreed with the applicant's approach [redacted]

With the exception of pending issue concerning the control of potential genotoxic impurity [redacted] in the starting material [redacted] the applicant has satisfactorily addressed all the drug substance-specific deficiencies. Given that any changes in synthetic pathway for the manufacture of starting material [redacted] and/or change of its vendor suppliers have potential of affecting the drug substance impurity profile, and thereby, the control strategies for manufacture of the drug substance, the applicant has been recommended to include a test and an appropriate acceptance criterion for [redacted] impurity in the specification for either the starting material, [redacted] or the drug substance, and provide details of analytical procedure used to measure residual levels of this impurity. Alternatively, the applicant can demonstrate that [redacted] is negative in an *in vitro* bacterial reverse mutation (Ames) assay.

In conclusion, from CMC perspective, this new drug application (NDA 204569) will be recommended for approval provided a) the applicant satisfactorily addresses the pending deficiency concerning control of potential genotoxic impurity, and b) Office of Compliance issues an acceptable recommendation for drug substance manufacturing and testing facilities.

III. Administrative.

A. Reviewer's Signature

Mohan Sapru

B. Endorsement Block

Senior Review Chemist:	Mohan K. Sapru, Ph.D.
CMC Branch Chief:	Ramesh Sood, Ph.D.
CMC Lead:	Martha Heimann, Ph.D.

B. CC Block

Project Manager:	Teshara Bouie.

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/s/

MOHAN K SAPRU
04/29/2013

RAMESH K SOOD
04/29/2013

OFFICE OF NEW DRUG QUALITY ASSESSMENT

Product Quality and Manufacturing Memo

Memo Date: 20-DEC-2012

From: Akm Khairuzzaman, Ph.D., Reviewer of the Drug Product
Mohan Sapru, Ph.D., Reviewer of the Drug Substance
On behalf of the CMC Review Team

Through: Ramesh Sood, Ph.D., Branch Chief Division I

NDA Number: 204569 GRMP Date: 18-FEB-2013
Applicant: Merck PDUFA Date: 30-MAY-2013

Drug Product Name and Strength: (b) (4) (suvorexant) Tablets, 15 mg, 20 mg, 30 mg and 40 mg

Drug Product Introduction:
(b) (4) (suvorexant) is an orally administered immediate release film coated tablet dosage form in four strengths namely 15 mg, 20 mg, 30 mg and 40 mg. (b) (4) Tablets, 15 mg, are white, oval, film-coated tablets with the Merck logo on one side and "325" on the other side, The 20 mg strength tablets are white, round, film-coated tablets with the Merck logo and "335" on one side and plain on the other side. (b) (4) Tablets will be packaged in all aluminum (aluminum-aluminum) blisters as a 30-count unit-of-use package.

The drug product is formulated using commonly used compendial excipients such as copovidone, lactose, microcrystalline cellulose, croscarmellose sodium, magnesium stearate and (b) (4) coating. (b) (4) (b) (4) (b) (4) The formulation composition is provided in Table 1.
The drug product manufacturing process was developed utilizing the concept of Quality by Design (QbD) so that the process can successfully deliver a product that can meet the target critical quality attributes (CQAs) such as content uniformity, assay, impurities/degredents, drug substance phase/form and stability, appearance, elegance, identity, and dissolution. In a nut shell the entire manufacturing process can be divided into two sub-section namely,

(b) (4)

The manufacturing schematic is outlined in Figure 1.

QbD Overview of the Drug Product:

The drug product, (b) (4) (suvorexant) was developed utilizing the concept of Quality by Design (QbD). The Applicant has defined the following QbD elements in the application:

(i) Target Product Profile (TPP): used for the development of the drug product and process

(ii) Critical Quality Attributes (CQAs): identified from the risk assessment. These are : content uniformity, assay, impurities/degredents, drug substance phase/form and stability, appearance, elegance, identity, and dissolution

(iii) Design Space (DS) established from DOE experiments during the product development for certain unit operation. See figure 2.

(iv) Control Strategy: (b) (4)

Drug Substance Introduction:

Background: The drug substance suvorexant, a new molecular entity (NME), is insoluble in water and has been classified as BCS Class II. Based on NDA 204569 submission, MSD International GmbH, Ballydine, Ireland (Establishment Registration # 3002807560) has been listed as the main facility responsible for manufacture, packaging and release testing of suvorexant drug substance. (b) (4) is a critical intermediate, which is provided to the drug substance manufacturing site by contract manufacturer (b) (4) who is responsible for manufacture, packaging and release testing (b) (4)

Synopsis of the Manufacturing Process: The applicant has used quality by design (QbD) approach to development of the drug substance manufacturing process. A flow diagram outlining the drug substance commercial manufacturing process is given in figure 3.

As outlined in the flow diagram, the drug substance is manufactured using a (b) (4) process. Compounds (b) (4) are designated as starting materials by the applicant. Manufacture of the intermediate (b) (4) is performed by a contract manufacture (b) (4) The (b) (4) is performed at the MSD International GmbH, Ballydine, Ireland.

Design Space and Proven Acceptable Ranges (PARs): Using quality by design (QbD) approach to development of the drug substance manufacturing process, the applicant claims to have used risk assessment and design of experiments (DOEs) strategies to define design space ranges for drug substance manufacturing steps, and identify critical quality attributes (CQAs). The drug substance CQAs indentified include a) description, b) identity, c) purity, and d) content of organic impurities and residual solvents (for details, refer to Appendix 2: Drug Substance Specification). The applicant seeks regulatory flexibility for movement within the proposed design space ranges. Parameters representing significant risk to drug substance CQAs at parameter settings outside the specified range are defined as critical process parameters (CPPs). Proven acceptable ranges have been defined as the ranges determined by traditional, single factor at a time development studies involving pilot or production scale batches. A summary of design space ranges and proven acceptable ranges is summarized in table 3, 4 and 5.

List of Sites:

Name of Sites	Operation	FEI Number
Schering Plough Products LLC, Pridco Industrial Park, State Road 183, Las Piedras, PR 00771, USA *Note*: See Table 9 for site specific high risk elements	Drug Product Manufacture	2650155
MSD International GmbH Ballydine, Kilsheelan, Clonmel, Co. Tipperary, Ireland. *Note*: See Table 10 for site specific high risk elements	Manufacture, Packaging and Release Testing of Suvorexant Drug Substance.	9610180300280 7560
(b) (4)	Manufacture, Packaging and Release Testing (b) (4)	(b) (4)

Drug Product Tables and Figures:

Table 1: Drug Product Formulation Composition

Strength:			15 mg	20 mg	(b) (4)
Component	**Quality Reference**	**Function**	**Amount per tablet (mg)**	**Amount per tablet (mg)**	
(b) (4)					
Suvorexant (MK-4305)	----	Active	15.00	20.00	
Polyvinylpyrrolidone/Vinyl Acetate Copolymer (Copovidone)	USP-NF, Ph. Eur., JPE			(b) (4)	
Lactose Monohydrate	USP-NF, Ph. Eur., JP				
Microcrystalline Cellulose	USP-NF, Ph. Eur., JP				
Croscarmellose Sodium	USP-NF, Ph. Eur., JP				
Magnesium Stearate (b) (4)	USP-NF, Ph. Eur., JP				
				(b) (4)	
Total Tablet weight			**195.5**	**258.8**	

Figure 1: Drug Product Process and In Process Control Flow Diagram

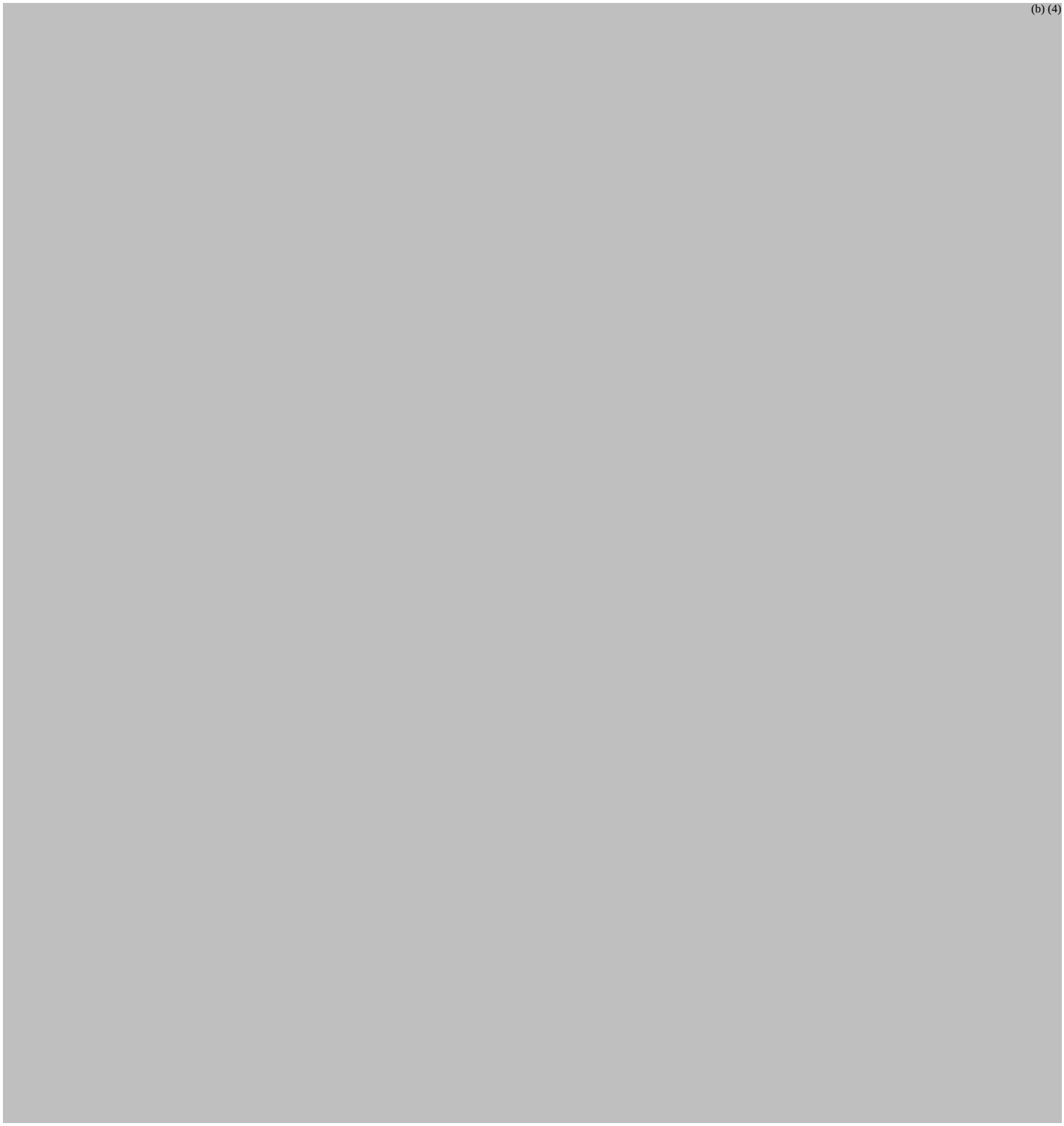

Figure 2: Drug Product Unit Operations and Respective Design Space (DS)

Table 2: Drug Product Specification

Tests	Acceptance Criteria	Test Methods
Appearance (release and shelf-life)	15 mg: White, oval, bi-convex, film coated tablet, Merck logo on one side and “325" on the other 20 mg: White, round, bi-convex, film coated tablet, Merck logo and "335" on one side and plain on the other	Test by visual observation
Suvorexant Assay (release and shelf-life)	(b) (4)	Assay, Degradates, & Identity by HPLC
Suvorexant Degradates (release and shelf-life)		Assay, Degradates, & Identity by HPLC
Suvorexant Dissolution (release and shelf-life)		USP Apparatus II and Assay by HPLC (Dissolution)
Dose Uniformity by HPLC (release)		Dose Uniformity (HPLC) & Identity (UV)
Identity (release) HPLC		Assay, Degradates, & Identity by HPLC
Identity (release) UV		Dose Uniformity (HPLC) & Identity (UV)
(b) (4)		(b) (4)
		Sec. 3.2.P.3.4.2.5

† (b) (4)

Drug Substance Tables and Figures

Figure 3: Synthetic scheme for Drug Substance

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/s/

AKM KHAIRUZZAMAN
12/20/2012
Product Quality and Manufacturing Memo for Facility Inspection

MOHAN K SAPRU
12/20/2012

MARTHA R HEIMANN
12/20/2012
for Ramesh Sood