

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204569Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 204569

SUPPL #

HFD #

Trade Name BELSOMRA

Generic Name Suvorexant 5mg, 10mg, 15mg and 20 mg oral tablets

Applicant Name Merck, Sharp & Dohme Corp.

Approval Date, If Known August 13, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES X NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES X NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES X NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO X

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO X

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO X

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval
AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently

demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2

YES

NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

!

!

IND #

YES

! NO

! Explain:

Investigation #2

!

!

IND #

YES

! NO

! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in

interest provided substantial support for the study?

Investigation #1 !
YES ! NO
Explain: ! Explain:

Investigation #2 !
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Cathleen Michaloski, BSN, MPH, RAC
Title: Senior Regulatory Project Manager
Date: 8.13.14

Name of Office/Division Director signing form: Ellis F. Unger, MD
Title: Office Director, ODE I

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

APPEARS THIS WAY ON ORIGINAL

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

/s/

CATHLEEN B MICHALOSKI
08/14/2014

ELLIS F UNGER
08/14/2014

Suvorexant Original Marketing Application
Debarment Certification

1

As required by §306(k)(1) of 21 U.S.C. 335a(k)(1), we hereby certify that, in connection with this application, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (Merck), did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.

Nadine Margarettten

Nadine Margarettten,
Ph.D.
Director
Worldwide Regulatory Affairs

August 9, 2012

Date

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See Tables 2 and 4	
	Suvorexant Original Marketing Application	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Nadine Margaretten	TITLE Director, Worldwide Regulatory Liaison
FIRM/ORGANIZATION Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.	
SIGNATURE <i>Nadine Margaretten</i>	DATE (mm/dd/yyyy) 08/09/2012

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, 420A
Rockville, MD 20850

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: BELSOMRA Established/Proper Name: suvorexant Dosage Form: 5, 10, 15 and 20 mg tablets, oral		Applicant: Merck, Sharp & Dohme Corp. Agent for Applicant (if applicable):
RPM: Cathleen Michaloski		Division: Division of Neurology Products (DNP), ODE I, CDER
<u>NDAs and NDA Efficacy Supplements:</u> NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)		<u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)): Provide a brief explanation of how this product is different from the listed drug. <input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)
<u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u> <u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u> <input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check: <u>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</u>		
❖ Actions <ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>August 14, 2014</u> • Previous actions (<i>specify type and date for each action taken</i>) 		<input type="checkbox"/> AP 8/13/14 <input type="checkbox"/> TA CR <input type="checkbox"/> None X CR 6/28/13

¹ The Application Information Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?</p> <p>Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received														
❖ Application Characteristics ³															
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority</p> <p>Chemical classification (new NDAs only):</p> <table> <tr> <td><input type="checkbox"/> Fast Track</td> <td><input type="checkbox"/> Rx-to-OTC full switch</td> </tr> <tr> <td><input type="checkbox"/> Rolling Review</td> <td><input type="checkbox"/> Rx-to-OTC partial switch</td> </tr> <tr> <td><input type="checkbox"/> Orphan drug designation</td> <td><input type="checkbox"/> Direct-to-OTC</td> </tr> </table>		<input type="checkbox"/> Fast Track	<input type="checkbox"/> Rx-to-OTC full switch	<input type="checkbox"/> Rolling Review	<input type="checkbox"/> Rx-to-OTC partial switch	<input type="checkbox"/> Orphan drug designation	<input type="checkbox"/> Direct-to-OTC								
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<p>NDAs: Subpart H</p> <table> <tr> <td><input type="checkbox"/> Accelerated approval (21 CFR 314.510)</td> </tr> <tr> <td><input type="checkbox"/> Restricted distribution (21 CFR 314.520)</td> </tr> </table> <p>Subpart I</p> <table> <tr> <td><input type="checkbox"/> Approval based on animal studies</td> </tr> </table> <table> <tr> <td><input type="checkbox"/> Submitted in response to a PMR</td> </tr> <tr> <td><input type="checkbox"/> Submitted in response to a PMC</td> </tr> <tr> <td><input type="checkbox"/> Submitted in response to a Pediatric Written Request</td> </tr> </table>	<input type="checkbox"/> Accelerated approval (21 CFR 314.510)	<input type="checkbox"/> Restricted distribution (21 CFR 314.520)	<input type="checkbox"/> Approval based on animal studies	<input type="checkbox"/> Submitted in response to a PMR	<input type="checkbox"/> Submitted in response to a PMC	<input type="checkbox"/> Submitted in response to a Pediatric Written Request	<p>BLAs: Subpart E</p> <table> <tr> <td><input type="checkbox"/> Accelerated approval (21 CFR 601.41)</td> </tr> <tr> <td><input type="checkbox"/> Restricted distribution (21 CFR 601.42)</td> </tr> </table> <p>Subpart H</p> <table> <tr> <td><input type="checkbox"/> Approval based on animal studies</td> </tr> </table> <p>REMS:</p> <table> <tr> <td><input type="checkbox"/> MedGuide</td> </tr> <tr> <td><input type="checkbox"/> Communication Plan</td> </tr> <tr> <td><input type="checkbox"/> ETASU</td> </tr> <tr> <td><input type="checkbox"/> MedGuide w/o REMS</td> </tr> <tr> <td><input checked="" type="checkbox"/> REMS not required</td> </tr> </table>	<input type="checkbox"/> Accelerated approval (21 CFR 601.41)	<input type="checkbox"/> Restricted distribution (21 CFR 601.42)	<input type="checkbox"/> Approval based on animal studies	<input type="checkbox"/> MedGuide	<input type="checkbox"/> Communication Plan	<input type="checkbox"/> ETASU	<input type="checkbox"/> MedGuide w/o REMS	<input checked="" type="checkbox"/> REMS not required
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<input type="checkbox"/> MedGuide w/o REMS															
<input checked="" type="checkbox"/> REMS not required															
Comments: Med Guide only															
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates														
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No														
❖ Public communications (<i>approvals only</i>)															
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action Press Office notified of action (by OEP) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> None <input checked="" type="checkbox"/> X HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> X Other – Health Advisory														
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 															

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

<p>Exclusivity</p> <ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDAs and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires:
<p>❖ Patent Information (NDAs only)</p> <ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	

- [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for each paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</p> <p>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
---	--

CONTENTS OF ACTION PACKAGE

Copy of this Action Package Checklist ⁴	X
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	X Included
Documentation of consent/non-consent by officers/employees	X Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) CR letter 6/28/14 and AP letter 8/13/14; AP replac ltr 8/14/14
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	8/7/14
• Original applicant-proposed labeling	8/29/12
• Example of class labeling, if applicable	X

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	7/9/14
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	2/14/14
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	7/14/14; 8/7/14
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • <i>Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</i> 	<input checked="" type="checkbox"/> acceptable 3/25/14 Review memo 4/17/13
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 11/5/12 <input checked="" type="checkbox"/> DMEPA 6/18/14 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 5/6/13 <input checked="" type="checkbox"/> ODPD (DDMAC) 6/1/13 <input type="checkbox"/> SEALD <input checked="" type="checkbox"/> CSS 4/26/13 6/12/13

Administrative / Regulatory Documents

<ul style="list-style-type: none"> ❖ Administrative Reviews (e.g., <i>RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte 	<input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	x Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>6/5/13</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	Full waiver; Peds Record ID: 2043 <input type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>) 	X Verified, statement is acceptable

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	<input checked="" type="checkbox"/> included
❖ Internal memoranda, telecons, etc.	<input checked="" type="checkbox"/> included
❖ Minutes of Meetings <ul style="list-style-type: none"> • Regulatory Briefing (<i>indicate date of mtg</i>) • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) • EOP2 meeting (<i>indicate date of mtg</i>) • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	<input checked="" type="checkbox"/> No mtg <input type="checkbox"/> N/A or no mtg EOR mtg 10/24/13 following 1 st cycle <input type="checkbox"/> No mtg 4/9/12 <input type="checkbox"/> No mtg
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> X AC meeting
<ul style="list-style-type: none"> • Date(s) of Meeting(s) • 48-hour alert or minutes, if available (<i>do not include transcript</i>) 	<input checked="" type="checkbox"/> May 20, 2013

Decisional and Summary Memos

❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None EB 7/18/14
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None RF 7/14/14
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> X None

Clinical Information⁶

❖ Clinical Reviews <ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) • Clinical review(s) (<i>indicate date for each review</i>) • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input type="checkbox"/> 7/9/14 <input type="checkbox"/> 6/21/13, 6/25/13 <input type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	<input type="checkbox"/> 8/9/12
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None Pulm. 6/13/13 Cardio-renal 4/5/13
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input type="checkbox"/> Not applicable 4/29/13 and 7/30/14
❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input type="checkbox"/> 6/28/13
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested 4/5/13

⁶ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology	X None
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics	<input type="checkbox"/> None
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None concurrence w/ reviewer memo
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/7/13 and 5/1/13
Clinical Pharmacology	<input type="checkbox"/> None
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None concurrence w/ reviewer memo
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 6/25/14, 12/12/13, 10/17/13, 6/24/13, 4/30/13
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	X None
Nonclinical	<input type="checkbox"/> None
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 6/19/13 and 5/9/13
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4/29/13 and 6/26/13
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input type="checkbox"/> No carc 1/24/13
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None 5/3/13, 6/24/13 Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	X None requested
Product Quality	<input type="checkbox"/> None
❖ Product Quality Discipline Reviews	
• ONDQA/OPB Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/29/14
• Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None concurrence w/ reviewer memo
• Product quality review(s) including ONDQA biopharmaceutics reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/3/14, 6/25/14, 12/12/13, 6/24/13, 12/20/12, 4/29/13, 4/30/13
❖ Microbiology Reviews	X Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (<i>indicate date of each review</i>)	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (<i>indicate date of each review</i>)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (<i>indicate date of each review</i>)	X None

Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>) (<i>all original applications and all efficacy supplements that could increase the patient population</i>)		See CMC reviews
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)		
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)		
❖ Facilities Review/Inspection		
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <u>NOT</u> include EER Detailed Report) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷</i>)		Date completed: 7/29/14 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (check box only, do not include documents)		<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

From: Michaloski, Cathleen
To: [Margaretten, Nadine](#); [Goodrow, Tamra L](#) (tamra_goodrow@merck.com)
Subject: N 204569 DEA scheduling
Date: Sunday, August 03, 2014 11:37:00 AM

Nadine and Tamra,

Controlled Substance Staff has asked that we convey this message to you:

We remind you of your agreement not to market suvorexant (Belsomra) until DEA finalizes scheduling under the Controlled Substances Act.

We do not expect any delays upon our final action, however, the reminder is required.

Thank you.

Cathleen Michaloski, BSN, MPH, RAC

*Sr. Regulatory Project Manager
Division of Neurology Products
FDA / CDER / OND / ODEI /DNP
White Oak Building 22 room 4342
301-796-1123
Cathleen.michaloski@fda.hhs.gov*

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/s/

CATHLEEN B MICHALOSKI

08/03/2014

Toure, Hamet

From: Toure, Hamet
Sent: Thursday, July 03, 2014 6:59 PM
To: nadine_margaretten@merck.com
Cc: Michaloski, Cathleen; Toure, Hamet
Subject: 204569_Advice memo

Dear Dr. Margaretten,

I am covering for my colleague, Cathleen Michaloski, today. Reference is made to NDA 204569. Reference is also made to your July 1, 2014, request for feedback regarding labeling. We find your proposed sentence, [REDACTED] (b) (4) acceptable.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4202
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
hamet.toure@fda.hhs.gov

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/s/

HAMET M TOURE

07/03/2014

From: Michaloski, Cathleen
Sent: Monday, June 09, 2014 2:45 PM
To: 'Margaretten, Nadine'
Subject: IR request - product packaging 204569
Importance: High

Good Afternoon Nadine:

Based on review of the re-submission, DMEPA recommends the following be implemented prior to approval of this application:

1. Wallet Labels: Professional Sample

a. Add dosing information similar to [REDACTED]

(b) (4)

[REDACTED] to the inside panel containing the tablets and to the Usual Dosage statement on the principal display panel to help prevent patients from administering all three tablets as one dose.

2. Blister Card Plastic Case Labeling and Carton Labeling: Retail

a. Increase the font size and prominence of the statement "Each tablet contains XX mg Suvorexant." Alternatively, consider revising the presentation of the strength statement to read "XX mg per tablet." This statement is more informative to the patient.

Please let me know if you have any questions. Thank you.

Cathleen Michaloski, BSN, MPH, RAC

Sr. Regulatory Project Manager

Division of Neurology Products

FDA / CDER / OND / ODEI /DNP

White Oak Building 22 room 4342

301-796-1123

Cathleen.michaloski@fda.hhs.gov

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/s/

CATHLEEN B MICHALOSKI

06/09/2014

Bouie, Teshara

From: Bouie, Teshara
Sent: Friday, May 16, 2014 9:33 AM
To: Margaretten, Nadine (nadine_margaretten@merck.com)
Cc: Michaloski, Cathleen
Subject: NDA 204569 - Information Request

Hi Nadine,

The provided dissolution data do not support the selection of your proposed dissolution acceptance criterion. Implement the following dissolution acceptance criterion for the 5 mg and 10 mg strengths of your proposed product and provide an updated specifications table for your product reflecting this recommendation.

- Q= ^{(b) (4)} in ^(b) min ₍₄₎

We request a response to this request by May 30, 2014.

Regards,

Teshara G. Bouie, MSA, OTR/L
CDR, United States Public Health Service
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of New Drug Quality Assessment I
Phone (301) 796-1649
Fax (301) 796-9749

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/s/

TESHARA G BOUIE

05/16/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 204569

PROPRIETARY NAME REQUEST CONDITIONALLY ACCEPTABLE

Merck Sharp & Dohme Corp.
126 Lincoln Avenue
P.O. Box 2000, RY33-208
Rahway, NJ 07065

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

Dear Dr. Margaretten:

Please refer to your New Drug Application (NDA) dated August 29, 2012, received August 30, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Suvorexant Tablets, 5 mg, 10 mg, 15 mg, and 20 mg.

We also refer to your:

- Class 2 resubmission, dated and received February 14, 2014, in response to our June 28, 2013, action letter
- Correspondence dated and received February 19, 2014, requesting review of your proposed proprietary name, Belsomra. We have completed our review of the proposed proprietary name, Belsomra and have concluded that it is acceptable

If any of the proposed product characteristics as stated in your February 19, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Ermias Zerislassie, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0097. For any other information regarding this application, contact Cathleen Michaloski, Regulatory Project Manager in the Office of New Drugs at (301) 796-1123.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

ERMIAS ZERISLASSIE

03/25/2014

TODD D BRIDGES on behalf of KELLIE A TAYLOR

03/25/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204569

**ACKNOWLEDGE –
CLASS 2 RESUBMISSION**

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:

We acknowledge receipt on February 14, 2014, of your February 14, 2014, resubmission to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for suvorexant (MK-4305) 5, 10, 15, and 20 mg Tablets.

We consider this a complete, class 2 response to our June 28, 2013 action letter. Therefore, the user fee goal date is August 14, 2014.

If you have any questions, call me, at (301) 796-1123.

Sincerely,

{See appended electronic signature page}

Cathleen Michaloski, BSN, MPH, RAC
Senior Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

CATHLEEN B MICHALOSKI

02/27/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204569 (IND 101847)

MEETING MINUTES

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 Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for suvorexant tablets, oral.

We also refer to the meeting between representatives of your firm and the FDA on September 27, 2013. The purpose of the meeting was to discuss your re-submission plans for NDA 204569.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-796-1123.

Sincerely,

{See appended electronic signature page}

Cathleen Michaloski, BSN, MPH
Sr. Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

Meeting Minutes
[Type A]

MEMORANDUM OF MEETING MINUTES

Meeting Type: End of Review Conference Type A
Meeting Date and Time: September 27, 2013, 12pm - 1pm EST
Meeting Location: White Oak Building 22 Room 1419
Silver Spring, MD 20993
Application Number: IND 101847, NDA 204569
Product Name: Suvorexant
Indication: Insomnia (sleep onset and/or sleep maintenance)
Sponsor/Applicant Name: Merck & Co., Inc.
Meeting Chair: Eric Bastings, M.D.
Meeting Recorder: Cathleen Michaloski, BSN, MPH

FDA ATTENDEES

Ellis Unger, M.D., Director, Office of Drug Evaluation I
Eric Bastings, M.D., Acting Director, Division of Neurology Products (DNP)
Ronald Farkas, M.D., Ph.D., Clinical Team Leader, DNP
Akm Khairuzzaman, Ph.D., Chemistry Reviewer, ONDQA
Mahesh Ramanadham, Ph.D., Office of Compliance, OMPQ
Sandra Suarez Sharp, Ph.D., Pharmacologist, Biopharmaceutics, ONDQA
Angela Men, M.D., Ph.D., Lead Pharmacologist, OCP
Cathleen Michaloski, BSN, MPH, Sr. Regulatory Project Manager

SPONSOR ATTENDEES

Scott Korn, M.D., Vice President, Regulatory Affairs
Tamra Goodrow, Executive Director, Regulatory Affairs
David Michelson, M.D., Vice President, Clinical Research, Neuroscience and Ophthalmology
Wm. Joseph Herring, M.D., Ph.D., Executive Director, Clinical Research, Neuroscience and Ophthalmology
Matthew Troyer, M.D., Executive Director, Clinical Pharmacology
Rebecca Wrishko, Ph.D., Senior Principal Scientist, Quantitative Sciences, PPDM Development
Stephanie Born, Ph.D., Senior Principal Scientist, Toxicology Sciences
Richard Briscoe, Ph.D., Senior Principal Scientist, Preclinical Development
Nadine Margaretten, Ph.D., Senior Principal Scientist, Worldwide Regulatory Group
Mohan Ganapathy, Ph.D., Executive Director, Global CMC Regulatory Affairs
Pramod Kotwal, Ph.D., Director, Global CMC Regulatory Affairs
Timothy Koester, B.S., Assoc. Director, Global CMC Regulatory Affairs
Rick Derrickson, B.S., Director, GPC Project Leadership
Andre Hermans, Ph.D., Assoc. Prin. Scientist, Chemistry, Analytical Development and Commercialization
Jessica Miller, Ph.D., Assoc. Director, Engineering, Pharmaceutical Commercialization Technology
Filippou Kesisoglou, Ph.D., Sr. Principal Scientist, Preclinical Development, Biopharmaceutics

1.0 BACKGROUND

New Drug Application (NDA) 204569 was submitted on August 30, 2012 for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance. A review of the suvorexant efficacy and safety data was completed by the Peripheral and Central Nervous System (PCNS) Drug Advisory Committee Meeting on May 22, 2013. On June 28, 2013, the FDA issued a Complete Response Letter, stating the application cannot be approved in its present form. Additionally, the Agency requested the following:

- 10 mg tablet must be available at time of approval as the starting dose and manufacturing data is needed to support the application;
- For patients expected to have significantly higher plasma levels of suvorexant (e.g. patients taking concomitant CYP3A4 inhibitors), a 5 mg tablet strength is needed;
- An updated label is required at the time of resubmission which incorporates information from the draft label prepared by the Agency in structured product labeling (SPL) format. The label in the resubmission is to have mark ups that show all changes by the Sponsor as compared with the draft label prepared by the Agency, as well as a clean copy in Word format and which includes annotations that support any proposed changes; and
- A safety update is required in the resubmission to include all data from nonclinical and clinical studies/trials under consideration, regardless of indication, dosage form, or dose level.

The objective of the meeting was to ensure a common understanding of the deficiencies in the Complete Response Letter received on June 28, 2013 and to obtain input and agreement on the Sponsor's plan to address the deficiencies. The meeting discussion focused on an appropriate resubmission plan allowing for review and approval of suvorexant (5 mg, 10 mg, 15 mg, and 20 mg tablet strengths).

2. DISCUSSION

2.1. Chemistry, Manufacturing and Controls

Question 1:

Does the FDA confirm that the proposed development plan and data package including in vitro dissolution and stability are sufficient to support review and approval of the 5 mg and 10 mg tablets?

FDA Preliminary Response:

Meeting Minutes
[Type A]

The proposed development plan and data package for 5 mg and 10 mg suvorexant tablets [REDACTED] (b) (4) is consistent with the proposal for 10 mg tablets discussed in the June 19, 2013, teleconference between Merck and FDA representatives. We agree that our previous agreement regarding the development plan and data package for the 10 mg tablet will extend to [REDACTED] (b) (4) 5 mg tablet. The adequacy of the data to support approval will be a matter for review. If development of a 5 mg tablet [REDACTED] (b) (4) becomes necessary, we recommend that you discuss the development plan and data package with the Agency.

Note that the approved dissolution method for the higher strengths can be implemented for the lower strengths provided the following requirements are met:

- The dissolution profiles for the 5 mg and 10 mg strengths do not differ significantly from the higher strengths in such a way that the discriminating ability is lost.

(b) (4)

- The setting of the dissolution acceptance criteria for these strengths should be based on the dissolution profile data collected from the registration/commercial/stability batches and may not be the same as that approved for higher strengths.

We remind you that if you are not planning on doing any dose proportionality studies to support the approval of these lower strengths, a waiver request of the CFR requirement to provide data from in vivo BA studies should be included in the NDA submission. The biowaiver will be granted if the following requirements are met:

- The proposed lower and higher strengths of your product have the same dosage form;
- The lower and highest strength products have the same manufacturing process; and
- Dissolution profile comparisons between the higher and lower strengths in three different pH media using the same dissolution mild testing conditions meet the f2 similarity requirements.

(b) (4)

Meeting Discussion:

Merck provided a status summary of the 5 mg and 10 mg tablet development, and informed FDA that the resubmission is planned for late first quarter 2014 depending on the quality data

Meeting Minutes
[Type A]

generated on the tablets over the next few months. Merck asked a follow-up question upon receiving the preliminary response. The question was: **Does the Agency agree that based on formulation and manufacturing characteristics with application of the IVIVC as described above, that an additional in vivo PK evaluation at the doses of 5 and 10 mg is not required?**

FDA responded to the clarification question stating that, as mentioned in previous discussions during the NDA 204569 review cycle, the IVIVC cannot be used as a surrogate for BA/BE given that it was a Level C correlation which only took into consideration Cmax. Under these conditions, the correlation could only be used to support the drug product specification ranges for some attributes [REDACTED] ^{(b) (4)}. Therefore, the approval of the lower strengths should be based on a dose-proportionally study. Alternatively, this study could be waived if the requirements stated in the preliminary comments are met. FDA suggested that if f2 testing fails, the Applicant may consider relying on *in vivo* data to justify/support the approval of these strengths in such a way that if dissolution of the new strengths (5 mg and 10 mg) using the QC method is demonstrated to be within the bounds established from pivotal clinical studies (e.g., 15 mg data from Protocol 051), a new PK study may not be required.

Merck asked whether demonstration of bioequivalence among the strengths would be required in the case where a dose-proportionally study is needed. The FDA mentioned that dose proportionality could be addressed by either applying the bioequivalence or the power model approaches.

If an additional *in vivo* PK evaluation (at the doses of 5 and 10 mg) is needed, then the dose proportionality of suvorexant in the dose range 5 to 20 mg can be assessed using a power model.

Question 2:

If development of a 5 mg tablet requires additional formulation development (incurring a significant delay compared to the 10 mg tablet) and differs from the other dose strengths (10 mg, 15 mg, and 20 mg), [REDACTED] ^{(b) (4)} then Merck would propose to provide a resubmission that would include data supporting only the new 10 mg tablet and appropriate precautionary labeling around use with moderate CYP3A inhibitors. Merck would also commit to a post approval submission of data supporting the 5 mg tablet.

- a. Does FDA agree that suvorexant can be approved with the 10 mg dose strength with appropriate label restrictions (e.g. statement that moderate CYP3A inhibitors are not recommended, as with the strong CYP3A inhibitors) [see Section 5.1.2] until a 5 mg dose strength is available for those receiving concomitant moderate CYP3A inhibitors?

FDA Preliminary Response:

This is acceptable.

Meeting Minutes
[Type A]

Meeting Discussion:

There was no additional discussion of this question.

- b. Does FDA agree with Merck's proposal to commit to a subsequent post-approval submission of data supporting the 5 mg tablet together with revised labeling in support of approval of the 5 mg tablet?

FDA Preliminary Response:

Yes, see response to 2a.

Meeting Discussion:

There was no additional discussion of this question.

2.2. Nonclinical and Clinical**Question 3:**

[REDACTED] (b) (4)

- a. Does the Agency agree that [REDACTED] (b) (4) can be provided in the submission [REDACTED] (b) (4)?

FDA Preliminary Response:

You will need to provide [REDACTED] (b) (4) if available at the time of the NDA submission and include [REDACTED] (b) (4) if available. No need to update the [REDACTED] (b) (4) information (summary tables, etc.) in CTD Module 2.7.2.

Meeting Discussion:

There was no additional discussion of this question.

- b. Does FDA agree that revisions to the clinical CTD sections (Module 2.5, 2.7.1-2.7.4 and integrated safety summaries) will not be required in the resubmission?

Meeting Minutes
[Type A]

FDA Preliminary Response:

Yes.

Meeting Discussion:

There was no additional discussion of this question.

- c. Does the FDA agree on the plan for inclusion of new nonclinical safety-related reports in the resubmission with appended Module 2.4, 4 and 2.6 modules?

FDA Preliminary Response:

Your plan for submitting the two new nonclinical studies to the NDA appears appropriate. If you would like us to consider the new pharmacology data on the effects of high doses of a different orexin receptor antagonist on rat sleep time duration in support of the application, then the full study report should be submitted to Module 4.

Meeting Discussion:

There was no additional discussion of this question.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items.

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/s/

ERIC P BASTINGS

10/24/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204569

**PROPRIETARY NAME
INCOMPLETE REQUEST**

Merck Sharp & Dohme Corp.
126 Lincoln Avenue
P.O. Box 2000, RY33-208
Rahway, NJ 07065

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

Dear Dr. Margaretten:

Please refer to your New Drug Application (NDA) dated August 29, 2012 , received August 30, 2012 submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Suvorexant Tablets, 15 mg, 20 mg, 30 mg, and 40 mg.

We also refer to your correspondence, dated and received April 23, 2013, requesting a review of your proposed proprietary name, Belsomra. Additionally, we refer you to the Complete Response letter dated June 28, 2013 in which you were requested to revise product characteristics (e.g., strength) to address the safe use of suvorexant. We have determined that your submission is incomplete because the product characteristics are not fully characterized based on deficiencies and recommendations cited in the Complete Response.

Once your product characteristics have been revised to address the deficiencies cited in Complete Response, you should submit a new request for a proprietary name review that includes all required information as detailed in the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>. Our review of your proposed proprietary name will not begin until we receive a complete submission.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Ermias Zerislassie, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0097. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Cathleen Michaloski, at (301) 796-1123.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST

07/22/2013

From: Michaloski, Cathleen
Sent: Tuesday, July 02, 2013 8:15 AM
To: 'Margareten, Nadine'
Subject: suvorexant labeling 204569
Importance: High

Nadine,

attached please find:

1. carton and container comments I mentioned to you last week.
2. the class labeling MG.
3. a clean version of the PI.

We hope you find this information helpful as you begin preparing your re-submission. If you have a time frame for when we might see the re-submission, please let me know. It would be helpful for our planning purposes.

Thank you.

Cathleen Michaloski, BSN, MPH

Sr. Regulatory Project Manager

Division of Neurology Products

FDA / CDER / OND / ODEI /DNP

White Oak Building 22 room 4342

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/s/

CATHLEEN B MICHALOSKI

07/03/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204569

DEFICIENCIES PRECLUDE DISCUSSION

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) submitted August 29, 2012, received August 30, 2012 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for suvorexant, oral tablets, 15, 20, 30 and 40 mg.

We also refer to our November 9, 2012, letter in which we notified you of our target date of June 1, 2013, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals And Procedures – Fiscal Years 2008 Through 2012."

As part of our ongoing review of your application, we have identified deficiencies that preclude discussion of labeling and postmarketing requirements/commitments at this time.

This notification does not reflect a final decision on the information under review.

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

Sincerely,

{See appended electronic signature page}

Jacqueline Ware, Pharm.D.
Chief, Project Management Staff
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

JACQUELINE H WARE

06/04/2013

From: Michaloski, Cathleen
Sent: Tuesday, May 28, 2013 3:36 PM
To: 'Margaretten, Nadine'
Subject: Information request from Clinical Pharmacology for NDA 204-569 Suvorexant

Importance: High

Good Afternoon,
We have an information request from Clinical Pharmacology for NDA 204-569 Suvorexant:

1. In the in vitro study (PK002), you investigated the induction potential of suvorexant on CYP1A2, CYP2B6 and CYP3A. You have not evaluated the induction potential of the major metabolite, M9. In the submission, you stated that since M9 was present in human hepatocytes as a predominant metabolite, the observed induction effects (on CYP isoforms in the hepatocytes treated with suvorexant) included the contribution (if any) of M9. The data suggesting the formation of M9 in hepatocytes seemed to be obtained from Study PK013 (in vitro metabolite profiling of MK-4305 in rat, dog, and human). Please provide further justifications how the results from this study, amount or concentration of M9 formed in human hepatocytes, reflects the in vivo situation, so that no separate study beyond Study PK002 is needed to evaluate the induction potential of M9 on CYP isozymes.

2. In the in vitro study (PK002) to evaluate whether suvorexant and its two metabolites were the substrates of P-glycoprotein, the apparent permeability was calculated using the following formula:

Papp = Transported amounts (pmol/3-hrs/well)/sum of the concentration in the donor and receiver compartments after 3-hrs incubation (nM)/surface area (0.11 cm²/well)/incubation time (10800 s).

Please provide your justification to use the sum of the concentration in the donor and receiver compartments at the end of incubation period. In general, the concentration used is the initial concentration of the test drug in the donor compartment (C₀).

3. In the in vitro study (PK002) to evaluate the induction potential of suvorexant on CYP3A4 mRNA expression, you used a RIS calibrated method with rifampicin used as the reference. You proposed that RIS value equal or larger than 1.0 may leads to clinical significant drug-drug interactions. Please provide your justification for this cut-off value, and whether your method was also validated using other inducers besides rifampicin.

Please respond within 1 week. Thank you.

Cathleen Michaloski, BSN, MPH
Sr. Regulatory Project Manager
Division of Neurology Products
ODE I/OND/CDER/FDA
301-796-1123

Room 4342 White Oak 22
10903 New Hampshire Ave.
Silver Spring, MD 20993
Cathleen.michaloski@fda.hhs.gov

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/s/

CATHLEEN B MICHALOSKI

05/29/2013

From: Michaloski, Cathleen
Sent: Wednesday, May 08, 2013 3:14 PM
To: 'Margaretten, Nadine'
Subject: Patient Labeling Comments - DMEPA- NDA 204569

Importance: High

Good Afternoon,

We have the following comments from the DMEPA patient labeling reviewer:

1. General Comments on all Labels and Labeling:

- a. The hue or intensity of the colors utilized for the strengths can make the labels and labeling for these strengths appear similar. Revise the hue or intensity of one color, or utilize multiple methods, such as presenting one strength in black font on a lighter background color to help differentiate the strengths.
- b. Add the controlled substance symbol for your final Schedule designation to the principal display panel of the labels and labeling in accordance with 21 CFR 1302.03 and 21 CFR 1302.04. Ensure the controlled substance symbol does not interfere with the readability of the proprietary name, established name, or strength.
- c. Replace the symbol ‘-’ with its intended meaning and add a unit of measure immediately follow all numbers as appropriate. For example, revise the storage statement ‘Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).’ to read ‘Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)’ to improve clarity.
- d. The proposed proprietary name *** was found unacceptable. Therefore, please replace the name with “Tradename” on label and labeling revisions until a conditionally acceptable tradename is granted.

2. Wallet Labels: Professional Sample

- a. Ensure the “FPO” image of the tablet on the principal display panel is replaced with an accurate picture of the tablet. The picture or image should reflect the true size, color, and imprint of the tablet.
- b. Revise the presentation of the strength statement to read “XX mg per tablet” on the front, inside, and back panels.
- c. On the inside panel containing the tablets, replace the statement with the statement “3 Tablets (XX mg each).” This statement is more informative to the patient and may help prevent patients from misinterpreting that all three tablets equal a mg strength of the

Suvorexant tablet.

d. Delete the statement “Each tablet contains XX mg Suvorexant” on the front panel, since it will be redundant to the revised strength statement of “XX mg per tablet.”

e. Add dosing information similar to [REDACTED] (b) (4) to the inside panel containing the tablets and to the Usual Dosage statement on the principal display panel to help prevent patients from administering all three tablets as one dose.

3. Blister Card Label: Retail

a. Label each blister with the proprietary name, established name, and strength. If the manufacturing process cannot accommodate this label, then multiple presentations of the proprietary, established name, and strength presented as “XX mg per tablet” should be displayed on the foil backing. This information could be presented in a horizontal, diagonal, or stacked format. However, ensure the proprietary name, established name, and strength can be read before the last blister is opened.

4. Blister Card Plastic Case Labeling: Retail

a. Revise the back panel to clearly convey the main intent of the label is to inform the end user how to gain access to the blister card and a tablet. Display a title on the back panel that conveys these messages similar to:

“Instructions: How to Open the Blister Card, and How to Remove a Tablet”

b. The blister card appears to be currently configured in a manner, in which an individual would need to push the tablets up through the foil. Thus, we recommend revising the third step of the instructions to read similar to “Push a tablet up through the foil.”

c. Add a fourth step to the instructions that instructs the patient to push in the inner tablet card after the tablet is removed. [REDACTED] (b) (4)

d. Decrease the size and prominence of or consider removing the proprietary name, established name, and strength statement on the back panel, so the end user can easily identify the principal display panel (front) and back panel.

e. Increase the font size and prominence of the statement “Each tablet contains XX mg Suvorexant.” Alternatively, consider revising the presentation of the strength statement to read “XX mg per tablet” as

recommended for the wallet label and removing the statement “Each tablet contains XX mg Suvorexant.”

- f. Ensure the “FPO” image of the tablet on the principal display panel is replaced with an accurate picture of the tablet. The picture or image should reflect the true size, color, and imprint of the tablet.
- g. Debolt the “Rx only” statement.

- h. On the principal display panel, remove the 2D Code FPO [REDACTED] (b) (4)

5. Carton Labeling: Retail

- a. Debolt the net quantity statement [REDACTED] (b) (4) and the “Rx only” statement since they are overly prominent. Additionally, revise the net quantity statement to read, “This package contains 30 Tablets in 3 Blister Cards. Each Blister Card contains 10 Tablets.” for clarity.

Thank you.

Cathleen Michaloski, BSN, MPH
Sr. Regulatory Project Manager
Division of Neurology Products/ODE I/CDER
ph 301-796-1123
Food and Drug Administration
email: cathleen.michaloski@fda.hhs.gov

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/s/

CATHLEEN B MICHALOSKI

05/08/2013

Executive CAC

Date of Meeting: April 2, 2013

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Karen Davis Bruno, Ph.D., DMEP, Alternate Member
Lois Freed, Ph.D., DNP, Supervisor
Richard Siarey, Ph.D., DNP, Presenting Reviewer

Author of Minutes: Richard Siarey

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #: 204-569

Drug Name: Suvorexant (MK-4305)

Sponsor: Merck and Co. Inc.

Background

Suvorexant is an orexin receptor antagonist being developed for the treatment of insomnia. The Sponsor conducted a 26-week study in TgrasH2 transgenic mouse and a 2-year carcinogenicity study in Sprague-Dawley rat. Protocols for these studies were submitted under IND 101847 and were reviewed by the ExeCAC (February 2, 2010 and June 16, 2009, respectively). The ExeCAC concurred with the Sponsor's proposed high dose for the mouse study but recommended adjustments to the lower doses, for both males and females. The Sponsor chose to conduct the mouse study at the originally proposed doses, except for an adjustment to the mid-high dose (increased from 125 to 200 mg/kg/day; the ExeCAC recommended 300 mg/kg/day). For the rat study, the Exec CAC concurred with the Sponsor's proposed doses for males but recommended adjustments to the lower doses for females. The Sponsor chose to conduct the rat study at the doses originally proposed for males and females.

Mouse Carcinogenicity Study

Suvorexant was administered by oral gavage to TgrasH2 mice at doses of 0, 0, 25, 50, 200, and 650 mg/kg/day for up to 26 weeks; both control groups received vehicle (hydroxypropyl methylcellulose-acetate succinate in 0.5% methylcellulose). The positive control (urethane, 1000 mg/kg/day) was administered i.p. on Days 1, 3, and 5. There was no significant difference in survival rate or marked changes in body weight gain between control and MK-4305 treated groups.

According to the Sponsor, there were no increases in the incidence of any tumor type in suvorexant-treated animals. According to the Agency's statistical evaluation, there was a significant positive trend in the incidence of hemangiosarcomas (combined across tissues) in females. However, according to the Exec CAC criteria, the incidence of hemangiosarcomas (combined across tissues) at the high dose in females was not

significantly increased compared to controls for a common neoplasm. The incidence was within the historical control mean (4.9%) and range (0-16%) for the conducting laboratory.

The expected increases in the incidence of lung (adenoma, adenocarcinoma) and spleen (hemangiosarcoma) were observed in urethane-treated animals.

Rat Carcinogenicity Study or Rat Dose Selection

Suvorexant was administered by oral gavage to Sprague-Dawley rats at doses of 0, 0, 80, 160, and 325 mg/kg/day to males and 0, 0, 40, 80, and 325 mg/kg/day to females for up to 104 Weeks; both control groups received vehicle (hydroxypropyl methylcellulose-acetate succinate in 0.5% methylcellulose). There was no difference in survival rate among groups; mean absolute body weight was reduced at the high dose in males (20%) and females (12%), compared to control, at the end of the dosing period.

Neoplastic findings consisted of increases in the incidence of thyroid follicular cell adenomas and combined adenomas/carcinomas at the high dose in females, of thyroid follicular cell adenomas at the mid and high doses in males, and of hepatocellular adenomas at the high dose in males.

Executive CAC Recommendations and Conclusions:

Mouse:

- The Committee found that the study was acceptable.
- Although the incidence of hemangiosarcomas was increased in high-dose females, the incidence was within the historical control range for the conducting laboratory. Therefore, the Committee concluded that these neoplasms were not clearly drug related.

Rat:

- The Committee found that the study was acceptable.
- The Committee concurred that the thyroid follicular cell adenomas and combined adenomas/carcinomas in high-dose females, thyroid follicular cell adenomas in mid- and high-dose males, and hepatocellular adenomas in high-dose males were drug related.

David Jacobson Kram, Ph.D.
Chair, Executive CAC

cc:\

/Division File, DNP
/LMFreed, DNP
/RSiarey, DNP
/CMichaloski, DNP
/ASeifried, OND IO

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/s/

ADELE S SEIFRIED
05/03/2013

DAVID JACOBSON KRAM
05/03/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204569

INFORMATION REQUEST

Merck Sharp & Dohme Corp.

Attention: Nadine Margaretten, Ph.D., Director, Worldwide Regulatory Affairs
126 Lincoln Avenue
P.O. Box 2000, RY33-208
Rahway, NJ 07065

Dear Dr. Margaretten:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Suvorexant Tablets.

We also refer to your March 11, 2013 and March 28, 2013, submissions, containing your response to our February 15, 2013, Information Request letter.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Substance

Based on your response to Drug Substance Comment 2 of our February 15, 2013, Information Request letter, we note that [REDACTED] (b)(4) was identified during your evaluation to contain structural alerts for potential genotoxicity. We acknowledge that no detectable levels [REDACTED] (b)(4) have been observed [REDACTED] (b)(4) in five batches of the starting material, [REDACTED] (b)(4). However, given that any changes in synthetic pathway for the manufacture of starting material 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, we recommend you include a test and an appropriate acceptance criterion for this impurity in the specification for either the starting material, [REDACTED] (b)(4) or the drug substance, and provide details of analytical procedure used to measure residual levels of this impurity. Alternatively, you may demonstrate that [REDACTED] (b)(4) is negative in an in vitro bacterial reverse mutation (Ames) assay.

Drug Product:

The data presented in your response dated March 28, 2013, demonstrates that the batches made [REDACTED] (b)(4) contains no detectable amounts [REDACTED] (b)(4). However, only one (1) out of twenty six (26) batches was manufactured [REDACTED] (b)(4). Moreover, this

batch was packaged [REDACTED] ^{(b)(4)} which is not the proposed marketed packaging for finished product. As a result, the Agency believes that you do not have enough data to support your assertion that batches manufactured [REDACTED] ^{(b)(4)} will have undetectable amounts [REDACTED] ^{(b)(4)} throughout the shelf life of the drug product. Therefore, the quality of the batches manufactured [REDACTED] ^{(b)(4)} cannot be assured [REDACTED] ^{(b)(4)} We recommend that you either:

- (i) Revise [REDACTED] ^{(b)(4)} or
- (ii) Include this specific test [REDACTED] ^{(b)(4)} in the drug product specification for batch release and stability.

If you have any questions, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Branch I, Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAMESH K SOOD

04/23/2013



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 204569

PROPRIETARY NAME REQUEST UNACCEPTABLE

Merck Sharp & Dohme Corp.
126 Lincoln Avenue
P.O. Box 2000, RY33-208
Rahway, NJ 07065

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

Dear Dr. Margaretten:

Please refer to your New Drug Application (NDA) dated August 29, 2012, and received August 30, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Suvorexant Tablets, 15 mg, 20 mg, 30 mg, and 40 mg.

We also refer to your correspondence, dated and received January 17, 2013, requesting review of your proposed proprietary name ^{(b) (4)}. We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

(b) (4)

(b) (4)

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review (See the Guidance for Industry, Complete Submission for the Evaluation of Proprietary Names,

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”).

³ IMS, Vector One®: National (VONA).Year 2012. Extracted March 22, 2013.

⁴  (b) (4) Audit. Years 2000-2012. Extracted March 22, 2013.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Laurie Kelley, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5068. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Cathleen Michaloski at (301) 796-1123.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST

04/17/2013

From: Michaloski, Cathleen
Sent: Tuesday, March 12, 2013 9:36 AM
To: 'Margarettten, Nadine'
Subject: N 204569 Request for information - Controlled Substance Staff

Importance: High

Good Morning Nadine,

We have the following request for information/comment from CSS:

1. In the human abuse potential study (study P025), the Bowdle VAS was used to assess perceptual effects following drug administration. Of the 13 VAS items that comprise the Bowdle VAS, please clarify which items are used to determine the composite scores of internal perception and external perception. Include details on how each measure (e.g. internal and external perception) are calculated.
2. Explain any missing data values in the human abuse potential study. For example, after receiving 30 mg zolpidem, several subjects did not report VAS values for overall drug liking at the early timepoints (e.g. the 0.5 min timepoint).

Please acknowledge receipt and provide a time frame for submitting this information.
Thank you.

Cathleen Michaloski, BSN, MPH
Sr. Regulatory Project Manager
Division of Neurology Products/ODE I/CDER
ph 301-796-1123
Food and Drug Administration
email: cathleen.michaloski@fda.hhs.gov

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CATHLEEN B MICHALOSKI

03/12/2013

From: Michaloski, Cathleen
Sent: Thursday, February 21, 2013 1:08 PM
To: 'Margaretten, Nadine'
Subject: Information request NDA 204569 Study 006 Data

Good Afternoon,

we have a request from the statistical review team:

Please submit subjective as well as PSG analysis datasets for study 006 which contain the efficacy data for both study periods.

We will need this data within a week's time; by Thursday 2/28/13.

Thank you.

Cathleen Michaloski, BSN, MPH
Sr. Regulatory Project Manager
Division of Neurology Products/ODE I/CDER
ph 301-796-1123
Food and Drug Administration
email: cathleen.michaloski@fda.hhs.gov

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/s/

CATHLEEN B MICHALOSKI

02/21/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204569

INFORMATION REQUEST

Merck Sharp & Dohme Corp.

Attention: Nadine Margaretten, Ph.D., Director, Worldwide Regulatory Affairs
126 Lincoln Avenue

P.O. Box 2000, RY33-208
Rahway, NJ 07065

Dear Dr. Margaretten:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Suvorexant Tablets.

We also refer to your December 20, 2012 submission, containing your response to our November 9, 2012, filing communication.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Substance

1. It is noted that you have provided revised figures outlining synthesis of proposed starting material [REDACTED] ^{(b)(4)} along with its specification and data [REDACTED] ^{(b)(4)}

[REDACTED]

2. Regarding the synthesis of starting material [REDACTED]

[REDACTED] ^{(b)(4)} both contain structural alerts for potential genotoxicity. Provide justification, with supporting data, for not including testing of their residual levels in the proposed specification for either [REDACTED] ^{(b)(4)} or the drug substance.

3. Regarding drug substance [REDACTED] ^{(b) (4)} specify the melting temperatures [REDACTED] ^{(b) (4)}
4. The provided description of the proposed manufacturing process includes several tentative options, which, as you have indicated, may or may not be used. [REDACTED] ^{(b) (4)}

We recommend you either remove reference to all the tentative options in manufacturing process description in section S.2.2 or alternatively, provide a description of trigger mechanisms and appropriate control strategies with adequate supporting data for all the specified options. Furthermore, to facilitate our evaluation of your overall control strategy, provide a detailed description of the manufacturing process that you intend to use for manufacture of the drug substance at a commercial scale.

5. We acknowledge that you have provided DOEs and experimental results that adequately support a majority of your proposed design space and proven acceptable ranges. However, regarding the tabulated design space and proven acceptable ranges provided in Table 1 (section S.2.2.5), several ranges, including ranges for critical process parameters, are open-ended ranges, which don't specify either the lower or the high limit values. Provide either the appropriate operating ranges for all the open ended ranges listed in Table 1 (section S.2.2.5) or a justification with supporting data for the open ended ranges.
6. Regarding [REDACTED] ^{(b) (4)} (with proposed acceptance limit [REDACTED] ^{(b) (4)}), provide batch analysis data for all the drug substance batches, including levels [REDACTED] ^{(b) (4)} that have been used for toxicological studies. In addition, specify the level at which [REDACTED] ^{(b) (4)} has been toxicologically qualified.
7. The level of heavy metals in drug substance is reflective of a variety of [REDACTED] ^{(b) (4)} operations and quality of materials used in the synthesis. Moreover, monitoring heavy metal content is a standard USP quality test. We recommend inclusion of heavy metal testing, according to the USP <231> method, in drug substance specification.

Drug Product:

Excipient variability:

1. Provide any available data [REDACTED] ^{(b) (4)}
[REDACTED] Update the excipient specifications with appropriate [REDACTED] ^{(b) (4)} limits, if necessary.

The (b) (4) Method:

2. Your control strategy

(b) (4)

is not supported by sufficient data.

(b) (4)

3. Provide data

(b) (4)

4. You propose

(b) (4)

5. Your proposed
sufficient data.

(b) (4) is not supported by
(b) (4)

6. We understand that the numerical changes
under your site quality system.

(b) (4) would be managed
(b) (4)

7. Your response to the agency's question # 4 sent out as a part of the 74 day letter comment
was found to be inadequate because of following reasons:

- (i) All experiments conducted to show the analytical method's
capability were done

(b) (4)

(b) (4)

- (ii) [REDACTED] (b) (4)
- (iii) The drug product contains [REDACTED] (b) (4) lactose
monohydrate and microcrystalline cellulose. [REDACTED] (b) (4)
Provide information/dat [REDACTED] (b) (4)
- (iv) In your response, you have concluded [REDACTED] (b) (4)
- (v) [REDACTED] (b) (4)

8. The in-process assay limits [REDACTED] (b) (4) are an important element of the control strategy. [REDACTED] (b) (4)

[REDACTED] (b) (4) Based upon the available information, we recommend that the limit be tightened [REDACTED] (b) (4)
[REDACTED] (b) (4) Alternatively, provide justification for the proposed limit.

9. Due to the above deficiencies [REDACTED] (b) (4) the provided analytical procedures for quantitative determination [REDACTED] (b) (4) in the drug product at any given time are not adequate. The Agency does not have an understanding on how [REDACTED] (b) (4) in the drug product may impact bioavailability. You have not shown any discriminating capability of your dissolution method to distinguish drug product [REDACTED] (b) (4)
- [REDACTED] Nor have you provided any data to show that the in vivo PK parameters will not be impacted [REDACTED] (b) (4). Therefore, in the absence of such data, include an appropriate validated test (and limit) in your [REDACTED] (b) (4) specification, as well as in the drug product specification, for the direct measurement [REDACTED] (b) (4). Justify the proposed limit on the basis of any possible impact on the bioavailability of the product.

(b) (4)
10. [REDACTED] (b) (4)

Film Coating Model

11. Coating process is delineated as a high risk process. The proposed [REDACTED] (b) (4) is found to be inadequate [REDACTED] (b) (4)

We recommend that you revise [REDACTED] (b) (4)

Stability:

12. You have not adequately responded to the agency's 74 day letter CMC comment # 8(g) which asked for the Drug Product's stability data [REDACTED] (b) (4)
- The Agency [REDACTED] (b) (4) understands that you have conducted stability studies [REDACTED] (b) (4) but you have not provided adequate data to demonstrate the stability of the finished product [REDACTED] (b) (4)
- Provide any available stability data [REDACTED] (b) (4) from batches manufactured [REDACTED] (b) (4)
- Alternatively, you may revise [REDACTED] (b) (4) based on available stability data.

13. Provide available data [REDACTED] ^{(b) (4)} during stability studies on the drug product. Include a specific test, and clinically relevant acceptance criteria, for the presence [REDACTED] ^{(b) (4)} in the drug product specification and stability protocol, or provide justification for exclusion of this test.
14. Provide available stability data from batches manufactured at the commercial site, Puerto Rico.

Batch record

15. In accordance with CFR 314.50 d(1)(ii)(c) complete description of the commercial scale drug product manufacturing processes is required and should include all process parameters. Therefore, include a master batch record and/or a detailed manufacturing process description in section P.3.3 of the application. The Agency recognizes that changes to non-critical process parameters can usually be managed under the firm's quality system without the need for regulatory review and approval prior to implementation. However, notification of changes including changes to process parameters should be provided in accordance with 21CFR 314.70.

Biopharmaceutics

1. Your proposal [REDACTED] ^{(b) (4)} is not acceptable. We have the following recommendations and requests:
 - a) In consistency with the ICH Q6A guidance [REDACTED] ^{(b) (4)}
[REDACTED]
we recommend the use of [REDACTED] ^{(b) (4)} dissolution testing to monitor for the amount [REDACTED] ^{(b) (4)} at release and on stability. For this purpose, provide information/data showing that your proposed dissolution testing methodology and proposed acceptance criterion are able to reject batches [REDACTED] ^{(b) (4)} Submit dissolution profiles [REDACTED] ^{(b) (4)} In addition, the setting of the acceptable amount [REDACTED] ^{(b) (4)} allowed by the dissolution acceptance criterion should be supported by clinical information (i.e., bioavailability, exposure-response, etc.).
 - b) Alternatively, monitor [REDACTED] ^{(b) (4)} at release and on stability using a sensitive analytical method [REDACTED] ^{(b) (4)} In addition, the setting of the acceptable amount [REDACTED] ^{(b) (4)} allowed by [REDACTED] ^{(b) (4)} specification should be supported by clinical information (i.e., bioavailability, exposure-response, etc.).
2. Your proposed dissolution acceptance criterion is based on IVIVC model predictions. However, since the model is NOT based on a "Level A" correlation and AUC is not part

of the correlation, it is uncertain if the proposed dissolution specifications will be able to reject batches that are not bioequivalent [REDACTED] (b) (4)

[REDACTED] we recommend that one of the following approaches be used for the setting of the dissolution acceptance criterion of your product:

- a) If you select to monitor [REDACTED] (b) (4) content [REDACTED] (b) (4) set the dissolution acceptance criterion based on the performance of the pivotal phase 3 clinical trial batches only. A wider dissolution acceptance criterion should be supported by BE studies.
 - o Submit the dissolution profile data (individual and mean values in tabulated and graphical form) from the pivotal phase 3 clinical batches.
- b) If you select to monitor [REDACTED] (b) (4) using dissolution testing, set the dissolution acceptance criterion based on the ability of the dissolution test to reject batches [REDACTED] (b) (4) (refer to our comments in 1a).

Also, when setting the dissolution acceptance criterion you need to take into consideration that Tmax plays an important role in the onset of action for this drug product. Since Tmax is dependent on the rate of in vitro and in vivo drug release, setting a specification at 30 min may allow for higher variability on the onset of action.

3. [REDACTED] (b) (4)
[REDACTED] Provide dissolution data supporting your proposed upper limit. In addition, provide data relating dissolution to D10, D50. Based on these dissolution findings, establish appropriate particle size limits (upper and lower bound for D10, D50 and D90).

4. The use [REDACTED] (b) (4)
[REDACTED] (b) (4) is not supported with data.
[REDACTED]
Therefore, [REDACTED] (b) (4)
provide justification on the use of dissolution [REDACTED]

5.

(b) (4)

(b) (4)

To address these issues provide dissolution profile comparisons with f2 testing/IVIVC predictions for any movements within your proposed design space for these two parameters.

If you have any questions, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Branch I, Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAMESH K SOOD

02/15/2013

From: Michaloski, Cathleen
Sent: Thursday, January 31, 2013 1:20 PM
To: 'Margarettten, Nadine'
Subject: Suvorexant: NDA 204569 information request/advice

Good Afternoon,

We have a comment from the safety labeling reviewer to convey to you:

We note in your submission, the primary blister card is packed inside a plastic case (b) (4)

If you have previously contacted (b) (4) regarding this issue and have documentation, please submit this information at this time.

Thank you.

Cathleen Michaloski, BSN, MPH
Sr. Regulatory Project Manager
Division of Neurology Products/ODE I/CDER
ph 301-796-1123
Food and Drug Administration
email: cathleen.michaloski@fda.hhs.gov

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CATHLEEN B MICHALOSKI

01/31/2013

From: Michaloski, Cathleen
Sent: Thursday, December 13, 2012 11:26 AM
To: 'Margarettten, Nadine'
Subject: NDA 204569 (suvorexant): further questions from CSS

Importance: High

Good Morning,

The CSS reviewer examined the dataset you submitted yesterday. Many data information are missing in this dataset (noting the difference between an efficacy study and an clinical abuse potential study). The reviewer has the following comments and requests.

1. The dataset did not include a variable “sequence” (SEQ), which is one of the fixed effects in the mixed-effects model.
2. Use treatment name instead of DOSE. For example, if TRT=A, then TRTNAME=suvorexant 40 mg. The variable DOSE can be dropped.
3. Define a variable VALN (numeric). Record the original data from each subject at each time point followed by the values from derived variables, for example, value of Emax, value of Emin, value of Tmax, etc. Use variable DTYPY to identify different parameters. For example, DTYPY=Emax. By using VALN and DTYPY, the variable Y can be dropped.
4. QSTPTNUM should include the time for predose response. For example, for High VAS, if the predose response was planned to be collected at hour -0.5, then -0.5 should be included for QSTPTNUM. Add an indicator variable to identify the predose response (the sponsor calls it BASE). By using QSTPTNUM, VALN and the indicator, variable BASE can be dropped.
5. Include the data from Qualification Phase in this analysis data set. Use variable APHASE (character) to identify the Treatment Phase or the Qualification Phase.
6. Define an indicator variable for completers. The completer is defined as a subject who finished 6 treatment periods.

Please reply asap as the clock is entering the 5th month and primary reviews need to be drafted. Thank you.

Cathleen Michaloski, BSN, MPH
Sr. Regulatory Project Manager
Division of Neurology Products/ODE I/CDER
ph 301-796-1123
Food and Drug Administration
email: cathleen.michaloski@fda.hhs.gov

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CATHLEEN B MICHALOSKI

12/13/2012

From: Michaloski, Cathleen
Sent: Thursday, December 06, 2012 11:08 AM
To: 'Margarettten, Nadine'
Subject: IR for NDA 204569 Suvorexant

Importance: High

Good Morning, we have an information request (IR) from DMEPA:

In your proposed insert labeling submitted on November 20, 2012, [REDACTED] (b) (4)

[REDACTED]. We acknowledge that information regarding these drug administration errors have been included in multiple clinical study reports as well as other sections of your previous submissions to the Agency; however, in order to assist our review process and ensure no information is overlooked, please provide one compiled document containing all of the details (including full text narratives describing the errors) of the drug administration errors noted in Table 1 of your proposed insert labeling. Given our review timelines, we request this information by COB Friday, December 14, 2012.

Thank you.

Cathleen Michaloski, BSN, MPH
Sr. Regulatory Project Manager
Division of Neurology Products/ODE I/CDER
ph 301-796-1123
Food and Drug Administration
email: cathleen.michaloski@fda.hhs.gov

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CATHLEEN B MICHALOSKI

12/06/2012

From: Michaloski, Cathleen
Sent: Tuesday, November 27, 2012 3:32 PM
To: 'Margarettten, Nadine'
Subject: Information request- CSS for NDA 204569

Nadine,

Regarding the review of NDA 204569, we have the following information request from the Controlled Substance Staff (CSS):

Please provide the source data for the human abuse potential study (reference P025) in ADaM format and include a data definition file. For more information, see the CDRISK Analysis Data Model (ADaM) Implementation Guidance:
<http://inside.fda.gov:9003/downloads/ProgramsInitiatives/Drugs/ComputationalScienceCenter/UCM211175.pdf>.

If you have any questions, do not hesitate to contact me. Thank you.

Cathleen Michaloski, BSN, MPH
Sr. Regulatory Project Manager
Division of Neurology Products/ODE I/CDER
ph 301-796-1123
Food and Drug Administration
email: cathleen.michaloski@fda.hhs.gov

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/s/

CATHLEEN B MICHALOSKI

11/28/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204569

FILING COMMUNICATION

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 29, 2012, received August 30, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Suvorexant, 10, 20, 30 and 40 mg oral Tablets.

We also refer to your amendments dated September 21, 2012, October 4, 2012 and November 2, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 1, 2013. In addition, we are currently planning to hold an advisory committee meeting to discuss this application in mid-May 2013.

At this time, we are notifying you that we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

INFORMATION REQUESTS

We request that you submit the following information:

Chemistry, Manufacturing and Controls

Drug Substance

1. Regarding control of drug substance manufacturing process, it is noted that design space ranges have been defined based on a series of design of experiments (DOEs). However, inadequate information is provided about the DOEs to support the proposed design space. To facilitate review of your proposed design space, provide the following information:
 - a. A summary description of DOEs used to develop design space. The description should, at a minimum, include a risk-based rationale for process parameter selection, a tabular summary of input and output data that show the multivariate combinations used and the statistical analysis of the DOE data showing statistical significance of the factors and their interactions.
 - b. A description of the approach, along with available supporting data, for scale up and verification of the design space at commercial scale.
2. Given that the proposed starting material [REDACTED] (b) (4) justify, with supporting data, the proposed designation [REDACTED] (b) (4) as the starting material. Furthermore, provide description of chemical steps used in [REDACTED] (b) (4) synthesis.

3. Provide data [REDACTED] (b) (4) concerning design of experiments to justify the proposed acceptance limits for individual impurities in the proposed starting materials [REDACTED] (b) (4)

Drug Product & Biopharmaceutics

4. You have not provided sufficient information to support control at batch release and upon stability [REDACTED] (b) (4)
[REDACTED] (b) (4) then provide a limit for the maximum percent [REDACTED] (b) (4) allowable in the drug product (at release and on stability). Also provide the analytical procedure (including their capability of quantitative limit) used to determine [REDACTED] (b) (4) along with appropriate validation data.
5. You may use dissolution testing to monitor for the amount [REDACTED] (b) (4) If you choose this alternative path, provide information showing that your proposed dissolution testing methodology and proposed acceptance criterion are able to reject for batches (at release and on stability) with an adequate amount [REDACTED] (b) (4) In addition, an

acceptable amount [REDACTED] ^{(b) (4)} needs to be supported by clinical information (i.e., bioavailability, exposure-response, etc.). Provide dissolution profiles [REDACTED] ^{(b) (4)}

6. Comment on [REDACTED] ^{(b) (4)} copovidone ^{(b) (4)}
[REDACTED] Indicate what grade of copovidone will be used in your formulation.
7. You have provided a design space [REDACTED] ^{(b) (4)}
[REDACTED] This is not consistent with ICH Q8 (R2) definition of design space. Propose a design space [REDACTED] ^{(b) (4)} consistent with ICH Q8 (R2) definition [REDACTED] ^{(b) (4)}
[REDACTED] Additionally, there is no [REDACTED] ^{(b) (4)} the impact they would have on product quality.
8. Insufficient information is provided to support the design space [REDACTED] ^{(b) (4)}
[REDACTED]
[REDACTED] therefore, to support the proposed control strategy [REDACTED] ^{(b) (4)} provide the following information:
- a. [REDACTED] ^{(b) (4)}
 - b. Data from DOE studies [REDACTED] ^{(b) (4)}
 - c. Data to demonstrate impact [REDACTED] ^{(b) (4)}
[REDACTED] What range [REDACTED] ^{(b) (4)}
have you evaluated in your multivariate analysis?
 - d. Indicate how you will be monitoring [REDACTED] ^{(b) (4)} during the commercial operation. [REDACTED] ^{(b) (4)}
[REDACTED] How will you recognize [REDACTED] ^{(b) (4)}

- and handle [REDACTED] (b) (4)
[REDACTED] during continuous manufacturing operation?
- e. Provide stability data [REDACTED] (b) (4)
- f. You have claimed [REDACTED] (b) (4)
[REDACTED] under both the accelerated and long term conditions. Clarify what were
the processing conditions used [REDACTED] (b) (4)
for these stability batches.
- g. What is the maximum proposed hold time [REDACTED] (b) (4) Provide
drug product stability data [REDACTED] (b) (4)
- h. Since you do not have any test [REDACTED] (b) (4) at batch release and for
the drug product stability, indicate [REDACTED] (b) (4)
[REDACTED] in the drug product upon storage.
- i. [REDACTED] (b) (4)
9. Insufficient information is provided [REDACTED] (b) (4) Provide data
[REDACTED] (b) (4)
[REDACTED] (b) (4)
Provide data [REDACTED] (b) (4)
in accordance with information provided.
10. Submit the input and output files generated using the IVIVC model for the prediction of
the [REDACTED] (b) (4) proposed limits. These data should be submitted as SAS Transport
files.

Nonclinical Comments

11. We appreciate that you have submitted nonclinical (including chronic toxicity,
reproductive and developmental toxicity, and carcinogenicity) studies with electronic

study data; however, CDER's preferred format for these studies is the SEND format. We ask that you provide, if possible, SEND formatted datasets for these and any future nonclinical studies.

Statistical Comments

12. Please clarify how you derived the subjective efficacy measure data, such as for subjective total sleep time in study P029, in the ADMD dataset from the raw SDTM datasets, representing the morning diaries. Which specific SDTM datasets and which specific variables are involved? Please provide your SAS code which creates the derived subjective efficacy measure data from the raw SDTM datasets that you have provided.

Physician's Labeling Rule (PLR) Format Issues

13. During our preliminary review of your submitted labeling, we have identified labeling format issues. The format issues are:

Adverse Reactions - Full Prescribing Information(FPI)

- When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Patient Counseling Information (Highlights and FPI)

- Comment: Do not number subsections.

We request that you resubmit labeling that addresses these PLR issues by November 26, 2012. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and Medication Guide, (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and Medication Guide (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Neurology Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request for a partial waiver of pediatric studies for children [REDACTED] (b) (4) this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

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

Sincerely,

{See appended electronic signature page}

Russell G. Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

RUSSELL G KATZ

11/09/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204569

NDA ACKNOWLEDGMENT

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:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Suvorexant (MK-4305) 15, 20, 30 and 40 mg Tablets

Date of Application: August 30, 2012

Date of Receipt: August 30, 2012

Our Reference Number: NDA 204569

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on OCTOBER 21, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the 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>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size.

Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, don't hesitate to contact me at (301) 796-1123.

Sincerely,

{See appended electronic signature page}

Cathleen Michaloski, BSN, MPH
Sr. Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

CATHLEEN B MICHALOSKI

09/13/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 101847

MEETING MINUTES

Merck & Co., Inc.
P.O. Box 2000, RY 33-208
Rahway, NJ 07065-0900

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

Dear Dr. Margaretten:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for suvorexant (MK-4305) for the treatment of insomnia.

We also refer to the March 19, 2012 Type B Pre-NDA meeting between representatives of your firm and the FDA, Division of Neurology Products. The purpose of the meeting was to discuss the pending submission of the NDA for suvorexant.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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

Sincerely,

{See appended electronic signature page}

Russell G. Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure



FOOD AND DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Date and Time: March 19, 2012
Meeting Type: Type B; Pre-NDA
Meeting Location: White Oak Bldg #22, Room 1421
Application Number: IND 101847
Product Name: MK 4305 Suvorexant (orexin receptor antagonist)
Sponsor Name: Merck & Co., Inc.
Meeting Requestor: Nadine Margaretten, Ph.D.
Meeting Chair: Russell Katz, M.D.
Meeting Recorder: Cathleen Michaloski, BSN, MPH

Meeting Attendees:

FDA Attendees:

Ellis Unger, M.D., Deputy Office Director, ODE I
Russell Katz, M.D., Division Director, Division of Neurology Products (DNP)
Ronald Farkas, M.D., Ph.D., Clinical Team Leader, DNP
Lois Freed, Ph.D., Supervisory Lead Pharmacology Toxicology, DNP
Angela Men, M.D., Ph.D., Supervisory Lead, Clinical Pharmacology OTS/OCP
Martha Heimann, Ph.D., Chemistry Lead, ONDQA
Angelica Dorantes, Ph.D., Biopharmaceutics, ONDQA
Kun Jin, Ph.D., Team Leader Statistics, OTS/DBI
Ohidul Siddiqui, Ph.D., Statistics, OTS/DBI
Kachikwu Illoh, M.D., MPH Clinical Reviewer, DNP
Melissa Banks-Muckenfuss, Ph.D., Pharmacology Toxicology Reviewer, DNP
Xinning Yang, Ph.D., Clinical Pharmacology Reviewer, OTS/OCP
Chad Ressig Ph.D., Controlled Substance Staff, OD
Antoine El-Hage, Ph.D., Division of Scientific Investigations, OC/OSI
Atul Bhattaram, Ph.D., Pharmacometrics, OTS/OCP
Yasmin Choudry, M.D., Office of Surveillance and Epidemiology, OSE/ DRISK
Tom Oliver, Ph.D., Pharmacology Fellow
Irene Z. Chan, PharmD., Team Leader, OSE/DMEPA
Julie Neshewat, PharmD, Safety Evaluator, OSE/DMEPA
Jared Lantzy, Regulatory Information Specialist, OBI/DDMSS
Cathleen Michaloski, BSN, MPH, Sr. Regulatory Project Manager, DNP

Sponsor Attendees:

Carole Sable, M.D., Vice President, Project and Pipeline Leader, Neuroscience and Ophthalmology
David Michelson, M.D., Vice President, Clinical Neuroscience and Ophthalmology
Wm. Joseph Herring, M.D., Ph.D., Senior Director, Clinical Neuroscience and Ophthalmology
Kathryn Connor, M.D., Director, Clinical Neuroscience and Ophthalmology
Neely Ivgy-May, Ph.D., Director, Clinical Neuroscience and Ophthalmology
Matthew Troyer, M.D., Senior Director, Clinical Pharmacology
Hong Sun, M.D., Ph.D., Director, Clinical Pharmacology
Rebecca Wrishko, Ph.D., Senior Investigator, Development; Pharmacokinetics, Pharmacodynamics and Drug Metabolism
Julie Stone, Ph.D., Senior Scientific Director, Modeling and Simulation
Dan Cui, Ph.D., Associate Director, Discovery; Pharmacokinetics, Pharmacodynamics and Drug Metabolism
Richard Entsuah, Ph.D., Executive Director, Late Development Statistics
Duane Snavely, M.A., Director, Late Development Statistics
Ellen Snyder, Ph.D., Associate Director, Late Development Statistics
Richard Briscoe, Ph.D., Therapeutic Area Lead, Toxicology
Stephanie Born, Ph.D., Senior Investigator, Toxicology Sciences
Tamra Goodrow, Ph.D., Senior Director, Worldwide Regulatory Affairs
Nadine Margaretten, Ph.D., Director, Worldwide Regulatory Affairs
John Renger, Ph.D., Neurosymptomatic Disorders Site Lead
Chris Winrow, Director, Ph.D., Psychiatry Research, Neuroscience Department
Ekopimo Okon Ibia, M.D., MPH, Director and US Regulatory Policy Lead

1.0 BACKGROUND

The purpose of the meeting was to discuss the content and format of the planned NDA for suvorexant (MK-4305) for the indication of insomnia in adults. Discussion focused on the following specific areas:

- Preclinical data package
- Clinical pharmacology and clinical data package
- Supportive documentation and electronic submission plans

2.0 SPONSOR QUESTIONS AND FDA RESPONSES

Questions Grouped by Discipline

Preclinical

The background package will provide a list of suvorexant non-clinical pharmacology and toxicology studies to be included in Module 2.4 and 2.6 of the NDA. The data include a specific evaluation for pharmacologically-mediated behavioral changes. Behavioral changes (transient limb buckling, unsteady gait, and/or recumbency observed following the presentation of a food treat) were observed in dogs administered suvorexant and other

orexin receptor antagonists. However, similar observations were not seen in non-human primates and have not been observed in clinical studies of suvorexant. Further evaluation of these dog behavioral changes using electrophysiological recordings and the Food Elicited Cataplexy Text indicate that the observed behavioral changes are consistent with increased sleep drive. Merck considers the behavioral changes to be specific to the dog, and the non-clinical findings to have been adequately evaluated.

Question 1:

Does the Agency agree that the non-clinical safety package as outlined is adequate to allow review of the NDA to support filing and approval of suvorexant, and does the agency have any preliminary questions regarding the rat carcinogenicity study report submitted in December 2011 or any other previously submitted non-clinical report?

FDA Preliminary Response:

- Your nonclinical safety package appears adequate to support filing of the NDA; however, the adequacy of the nonclinical studies will be a matter of review. We remind you that each pivotal nonclinical study must include a separate, signed and dated Pathology Report.
- At this time, we have no additional comments on your nonclinical studies.

Meeting Discussion:

The sponsor indicated that study reports for all pivotal toxicology studies will contain signed and dated Pathology Reports.

Clinical

Clinical Pharmacology:

A comprehensive set of clinical pharmacology studies has been conducted to address the safety and tolerability, PK, and PD of suvorexant. An overview of the clinical pharmacology program (see Section 5.2) with the proposed table of contents for Modules 2.7.1 (Summary of Biopharmaceutic Studies and Associated Analytical Methods – see Section 6.2) and 2.7.2 (Summary of Clinical Pharmacology Studies– see Section 6.3) of the NDA is summarized in the Background Package. The PK and exposure-response modeling plan(s) is also summarized in the Background Package.

Question 2:

a. Does the Agency agree that the content and presentation of the clinical pharmacology program will be adequate to allow review of the NDA in support of filing and approval of suvorexant?

FDA Preliminary Response:

Overall, the clinical pharmacology program appears acceptable provided the following information is submitted in the NDA package.

Please confirm that the formulation used in the pivotal Phase 3 trials was the to-be-marketed formulation (TMF). In addition, please clarify to what extent the TMF is different from the preliminary market formulation 2 (PMF2, P2) which was used in the majority of the clinical pharmacology studies.

Additional Clinical Pharmacology Recommendations:

- 1) The dose of suvorexant used in study 008 was 4 mg; however, in the forest plot (Figure 3, section 5.2.3), it was shown as 40mg. Please clarify.
- 2) We recommend that you conduct a clinical study in severe hepatic impairment patients.
- 3) Please provide justification for the following:
 - a) why the *in vivo* induction potential of suvorexant on CYP2B6 is considered low. The effect of suvorexant on midazolam could be the net result of inhibitory and induction effects. Thus, the results from the midazolam DDI study may not be readily applied to interaction of suvorexant with CYP2B6 substrates.
 - b) why is the *in vivo* inhibition potential of suvorexant on OATP and BCRP considered low? Please refer to the newly updated FDA Guidance for Industry: Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.

(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>)
- 4) We recommend that you conduct *in vitro* studies to evaluate the inhibition potential of M9 on CYP2C8 and CYP2C19, its induction potential on CYP2B6 and CYP1A2, and its inhibition potential on transporters (BCRP, OATP1B1, OATP1B3).
- 5) Suvorexant is a highly protein bound drug (99%). Please provide information on what kind of protein(s) it binds to.
- 6) Please provide the Clinical Pharmacology Review Aid in the NDA submission (see the attachment).

Meeting Discussion:

The sponsor confirmed that the to-be-marketed formulation (TMF) was used for the pivotal trials. The sponsor stated that there were only minor changes between the TMF and PMF2 formulations and such changes meet SUPAC level 1/2 criteria. The sponsor clarified that 40 mg suvorexant for Study 008 with ketoconazole in the forest plot was an error, and should be 4 mg of suvorexant.

The sponsor does not intend to conduct the clinical study in patients with severe hepatic impairment. They claimed that although suvorexant is metabolized by the liver, per the findings, no significant PK changes were observed for the patients with moderate hepatic impairment, and that the study in severe hepatic impaired patients is not required. The sponsor proposed addressing severe hepatic impairment through labeling, indicating that suvorexant should be used “with caution” in severe hepatic impairment. The Division asked the sponsor to provide justification for why the study in severe hepatic impairment is not needed, and the sponsor agreed to include it in the NDA submission.

The sponsor will provide detailed information about the relevant in-vitro studies (2B6, OATP and BCRP) in the NDA, and will justify why the induction/inhibition potentials are low. In addition, the sponsor clarified that suvorexant is bound to both albumin and alpha-1-acid glycoprotein, and that there is no concentration dependency for suvorexant protein binding.

b. Does the Agency agree with the Sponsor's PK and exposure-response modeling plan to permit review of the NDA in support of filing and approval of suvorexant?

FDA Preliminary Response:

All datasets used for model development and validation should be submitted as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

A model development decision tree and/or table should be submitted which gives an overview of modeling steps.

For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

Meeting Discussion:

The sponsor acknowledged these comments and there was no further discussion.

Clinical Development:

The late phase Clinical Development Program for suvorexant consists of one Phase 2b dose-finding trial (Protocol 006, previously discussed at the End of Phase 2 meeting) and three Phase 3 trials: one long-term safety trial (Protocol 009) and two confirmatory efficacy trials (Protocols 028 and 029). The background package provides an overview of the clinical development program, which was designed to demonstrate the efficacy and safety of suvorexant for the indication of insomnia with no short-term use restriction (see Section 5.3). These studies were conducted as multicenter, multinational trials and included adult patients \geq 18 years of age.

The clinical development section of the background package includes the following:

- High level Table of Contents for CTD sections 2.5, 2.7.3 and 2.7.4 (Sections 6.1, 6.4, and 6.5).
- Shells for the ISE and ISS CTD documents (which detail the strategy for analysis and planned presentation of results across trials, and reflect content that will be summarized in 2.7.3 and 2.7.4 – see Appendixes 8.2 and 8.3);
- Shell for the CSR of Protocol 029 (one of the confirmatory efficacy trials – see Appendix 8.1);
- Preliminary results from the recently completed long-term safety trial (Protocol 009 – see Appendix 8.5);
- Preliminary results from the recently completed Phase 3 pivotal efficacy/safety trials (P028 and P029 – see Appendices 8.6 and 8.7);
- The iSAP for the ISE was previously submitted on November 15, 2010, Serial No. 126. In addition to the plans detailed in the protocols and iSAP, analyses of subjective wake time after sleep onset (sWASOM) will be provided in the confirmatory efficacy CSRs and in the CTD in the same manner as subjective total sleep time (sTSTM), to provide a supportive analysis for evaluation of sleep maintenance efficacy (as agreed to by FDA on June 2, 2011 per FDA Memorandum of Telephone Conference);
- The iSAP for the ISS (see Appendix 8.10), and
- A summary of expected exposure by age, by dose, and duration.

Question 3:

Based on the Background Package, Table of Contents for the CTD sections 2.5, 2.7.3, 2.7.4, the ISE shell, the ISS shell, the iSAP for Efficacy, and the iSAP for Safety:

Does the Agency agree that the planned organization and presentation of individual and pooled efficacy and safety results from the suvorexant clinical development program are adequate to support the filing and review of suvorexant for the treatment of insomnia?

FDA Preliminary Response:

Your planned organization and presentation of the efficacy and safety results appear adequate for filing of the New Drug Application. Also, we agree with your plan to provide analyses of subjective wake time after sleep onset (sWASOM) in a manner that enables us to assess sWASOM and objective WASO as co-primary endpoints for sleep maintenance efficacy. We can only determine that the overall package is sufficient for filing purposes after we receive your entire NDA submission.

Also, we expect you to include in your analyses of adverse experience information on incidence of complex sleep-related behaviors and sleepwalking, as well abnormalities of vital signs and laboratory testing that are related to the drug treatment.

Meeting Discussion:

There was no further discussion of this question.

Abuse Potential Assessment and Scheduling: Merck will conduct an integrated summary of abuse potential with data from non-clinical studies and from clinical trials involving human subjects and patients with insomnia. To aid the Controlled Substance Staff's (CSS's) analysis of abuse potential, this assessment and a scheduling recommendation will be discussed in an 8-Factor Analysis of Abuse Potential as a separate report in the NDA in Module 5.3.5.3. A summary of this report will be included in relevant sections of the CTD (e.g. Modules 2.7.4 and ISS). The table of contents for the 8-Factor Analysis of Abuse Potential is included in the PreNDA Background Package (see Section 6.10). For the abuse liability assessment from clinical trials of suvorexant, AE terms suggesting potential for abuse will be specifically evaluated. A list of such terms is included in the draft ISS shell; input on this list of AE terms was incorporated based from Agency feedback from two meetings: End of Phase 2b (held November 5, 2009) and CSS meeting on abuse potential assessment (held March 2, 2010).

Merck wants to enable a timely scheduling review of suvorexant and is committed to working with the Agency during the NDA and scheduling reviews. During the NDA review and before the NDA Action Date, Merck understands that the CSS will target to submit the scheduling recommendation to the Assistant Secretary of Health (ASH, in the Department of Health and Human Services) for forwarding to the Drug Enforcement Administration (DEA). Upon NDA submission, Merck will request that the Agency inform us when the CSS submits the scheduling recommendation to ASH.

Question 4:

Does the Agency concur that the planned approach for assessment of suvorexant's abuse potential, inclusive of the formal abuse liability trial results, plans for presentation of program-wide abuse-related AEs, and the planned content and format of the 8-Factor Analysis of Abuse Potential, is sufficient to facilitate an expeditious scheduling decision?

FDA Preliminary Response:

- The FDA assessment of abuse potential of a drug is a review issue. Our conclusions, evaluations, and recommendations begin after you submit the NDA and FDA accepts it for filing.
- Overall, the proposed format and structure of the abuse potential section in the NDA appears adequate. See the draft *Guidance for Industry-Assessment of Abuse Potential of Drugs* (Jan 2010) for advice on the format and structure of the abuse potential section in the NDA and the eCTD format.
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>
- An eight factor analysis is not required in the NDA. However, you must submit a description and analysis of studies or information related to the abuse potential of MK-4305, including a proposal for scheduling.
 - An eight factor analysis is a legal document that contains information that is different from the abuse potential section of the NDA.

Meeting Discussion:

The Sponsor proposed to submit their scheduling proposal in module one of the eCTD, with the understanding that an eight factor analysis was not required in the NDA submission. CSS concurred with this approach.

Other Clinical and Data-Related Questions:

CSR Shells: A CSR shell for Protocol 029, is provided in Appendix 8.1 of this background package. The Clinical Study Reports will be in alignment with ICH E3.

Question 5:

Does the Agency concur that the planned format of the Phase 3 CSRs (as illustrated by the CSR shell for Protocol 029, one of the confirmatory efficacy trials) is acceptable to support the review of the NDA?

FDA Preliminary Response:

We agree with the planned format of the phase 3 CSRs

Meeting Discussion:

There was no further discussion of this question.

Label Components: Label components are listed in the Table of Contents in the Background Package (see Section 4). The Patient Product Information (PPI) will describe the benefits and risks with the product.

Question 6:

Please confirm that the proposed labeling components meet requirements for products in this indication.

FDA Preliminary Response:

In general, the labeling components that you present resemble those of other products for insomnia. However, it is not clear whether the indication sought is for both sleep onset and sleep maintenance or either of the components. A final determination on this labeling issue can only be made upon review of the NDA.

Meeting Discussion:

There was no further discussion of this question.

Office of Scientific Investigations (OSI) and Audit Preparation for Clinical Sites:

Merck has a proposal in the PreNDA background package for producing site level datasets to aid OSI in identifying clinical trial sites for inspections for the two confirmatory efficacy studies (Protocols 028 and 029 – see Section 7.5). This proposal is consistent with the FDA document "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" with two exceptions:

- Financial disclosure information will not be included in the summary level dataset since this information is sensitive and has extremely limited distribution within Merck. Note that this information is provided by a separate group within Merck and will be provided to FDA within a section of the NDA.
- Data related to the location of and contact information for each site will not be included in the site level dataset. This information will be provided only for the sites that are identified for audit by the OSI. This approach will allow Merck to provide accurate site address/contact information e.g., in the event that it has changed since the time of trial reporting) immediately prior to any site visits by OSI staff. Once OSI has selected sites for inspection and informed Merck, Merck will submit site specific individual data listings.

Question 7:

a. Does the Agency agree that the proposal summarized in the background package will satisfy OSI requirements?

FDA Preliminary Response:

Submission of the financial disclosure information in the application meets regulatory requirements. However, it is your decision whether to provide this information in the requested format for use in the site selection tool.

Submission of sites information (location and contact information) meets regulatory requirements. However, it is your decision whether to provide this information in the requested format for use in the site selection tool.

Meeting Discussion:

The sponsor agreed that the information requested will be provided only for the selected sites identified by OSI for audit. The sponsor declined participation in the pilot program.

b. Can the Agency provide a current version of the document "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" in advance of the preNDA meeting?

FDA Preliminary Response:

Yes, we will provide you with a current version of the documents in advance of the Pre-NDA meeting (attached at end of comments).

Meeting Discussion:

There was no further discussion of this question.

Plans for Electronic Submission Deliverables:

Case Report Tabulations (CRTs)

A mixed data format NDA submission is planned. Phase 1 data will be provided with non-SDTM format SAS transport files along with define.pdf file and blank annotated CRFs, compliant with the 1999 FDA Guideline (Computerized Systems Used In Clinical Trials). The Phase 2 and 3 data will be provided as SAS transport files in SDTM format along with a define.XML file and blank annotated CRFs, with the exception of power spectral data which will be provided in non-SDTM format SAS transport files along with define.pdf file.

Question 8:

Does the Agency concur with the submission plans for CRTs?

FDA Preliminary Response:

We agree with the plans for the Case Report Tabulations.

Meeting Discussion:

There was no further discussion of this question.

Electronic Case Report Forms (eCRFs):

Merck plans to submit Electronic Case Report Forms for any patients who died (CRF Category 1) and who discontinued due to AE (CRF Category 2) consistent with CFR 314.50. Merck also plans to submit eCRFs needed to support the CSS in the scheduling

assessment of suvorexant including Category 3 (subjects who discontinued due to any other reason other than an adverse event) and subjects with AEs relevant to scheduling considerations (abuse potential, residual effects, and withdrawal). Please refer to Section 5.3.2 of this Background Package for more details.

Question 9:

Please confirm that submission of eCRFs for Categories 1 and 2 as well as to support the CSS scheduling assessment is sufficient for the NDA.

FDA Preliminary Response:

This is acceptable. Also, the Division may request CRFs for SAEs of particular interest in the course of review if the need arises.

Meeting Discussion:

There was no further discussion of this question.

Statistical Review Aid (SRA):

Merck proposes to submit a statistical review aid (SRA) package for the Phase 3 trials in the NDA; this includes two confirmatory efficacy trials (Protocols 028 and P029) and a long-term safety trial (Protocol 009). The SRA package will include the following information related to analyses of the primary and/or secondary efficacy hypotheses as well as key supportive analyses (e.g., sWASOM): a) define.pdf which contains data definitions (metadata) of the analysis data sets and variables; b) analysis data sets; c) analysis programs; and d) a reviewer's guide which describes how to set up and use the SRA.

Question 10:

Merck believes that the Statistical Review Aid package described above will provide adequate information to the Reviewers for the evaluation of efficacy from the two confirmatory efficacy trials (P028 and P029) and the long-term safety trial (P009). Does the Agency agree with the scope and high-level content of the package described above?

FDA Preliminary Response:

The Statistical Review Aid package as described above is adequate for a formal statistical review of the two confirmatory efficacy trials (Protocols 028 and 029).

Meeting Discussion:

There was no further discussion of this question.

Financial Disclosure:

Financial Disclosure information will be provided for the Phase 2 and 3 trials for the NDA: Phase 2b trial P006, and Phase 3 Protocols 009, 028, and 029.

Question 11:

Please confirm that the list of trials for which we will provide financial disclosure information is acceptable. If the Agency desires financial disclosure information for any other trials, please identify the trials.

FDA Preliminary Response:

The plan to provide financial disclosure information for the phase 2 and 3 trials appears acceptable.

Meeting Discussion:

There was no further discussion of this question.

Pediatric Assessment:

At the suvorexant End of Phase 2 Meeting held on November 5, 2009, the Agency concurred with Merck's plans [REDACTED] (b) (4). Merck submitted [REDACTED] (b) (4) to the Investigational New Drug (IND) on July 26, 2011 (Serial No. 0155) [REDACTED] (b) (4).

On October 31, 2011, the Division responded [REDACTED] (b) (4).

[REDACTED] (b) (4) The Division also provided several preliminary comments [REDACTED] (b) (4) in their response.

Question 12:

[REDACTED] (b) (4)

a. Does the Agency concur with the [REDACTED] (b) (4) proposed [REDACTED] (b) (4)

FDA Preliminary Response:

[REDACTED] (b) (4)
We will (b) (4)
have to review the NDA package [REDACTED].
Therefore, the scope and timing of the studies are subject to further discussion based on
[REDACTED] (b) (4) that you submit in the NDA.

Meeting Discussion:

The sponsor acknowledged the Division's response and requested clarification on the timing of the submission [REDACTED] (b) (4). The Division responded [REDACTED] (b) (4)
[REDACTED] and reiterated that the sponsor needs to submit in its NDA package [REDACTED] (b) (4) for the Division to review. Further, the extent and timing [REDACTED] (b) (4) will be determined upon review of the NDA.

b. Does the Agency concur with a waiver for children [REDACTED] (b) (4)

FDA Preliminary Response:

Yes, we are likely to agree to waiver for children [REDACTED] (b) (4), although a final decision can not be made at this time.

Meeting Discussion:

There was no further discussion of this question.

c. Does the Agency agree on the [REDACTED] (b) (4) revision for Agency review (i.e. after approval of the original NDA)?

FDA Preliminary Response:

The [REDACTED] (b) (4) may be revised following further discussion with the Division and review of your NDA.

Meeting Discussion:

See above response to Question 12a.

3.0 ACTIONS ITEMS:

None noted.

4.0 ATTACHMENTS AND HANDOUTS

Appendices:

1. Division of Scientific Investigations:

Please note the requested information is Optional/Voluntary.

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct the inspections (Item I and II).

The dataset that is requested as per Item III below, is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

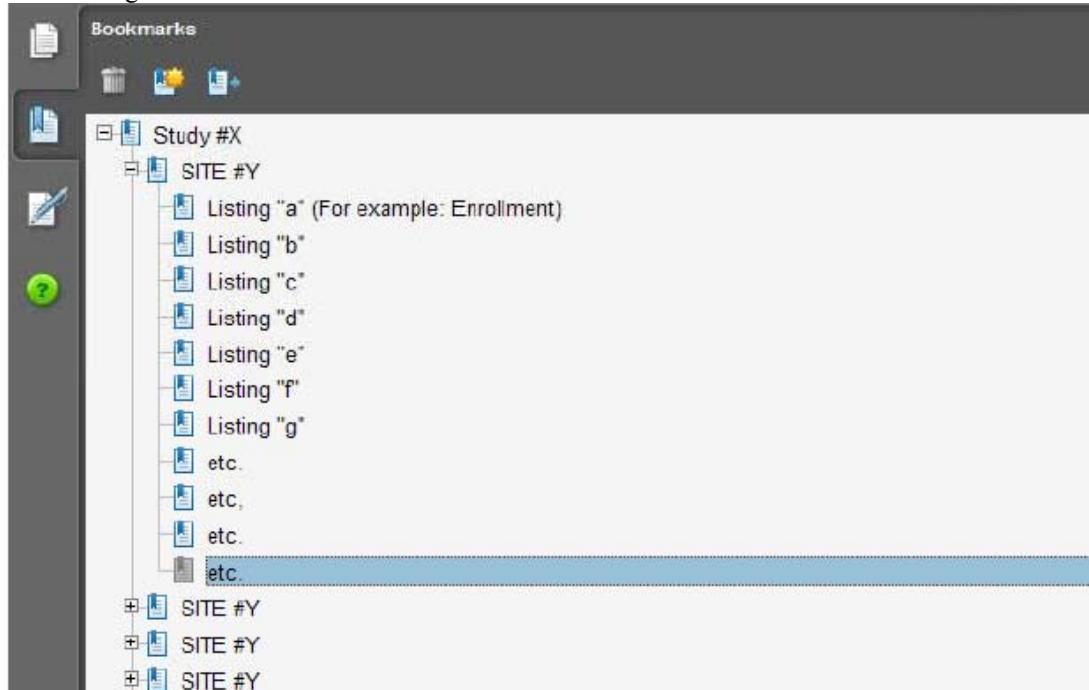
I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3 clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Current Location of Principal Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
2. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:
 - a. Number of subjects screened for each site by site
 - b. Number of subjects randomized for each site by site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:
 - a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
 - b. Name, address and contact information of all CROs used in the conduct of the clinical trials

- c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
 - d. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)
4. For each pivotal trial provide a sample annotated Case Report Form (if items are provided elsewhere in submission, please describe location or provide a link to requested information).
 5. For each pivotal trial provide original protocol and all amendments (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data (“line”) listings. For each site provide line listings for:
 - a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
 - b. Subject listing for treatment assignment (randomization)
 - c. Subject listing of drop-outs and subjects that discontinued with date and reason
 - d. Evaluable subjects/ non-evaluable subjects and reason not evaluable
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of laboratory tests performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to Attachment 1, “Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions” for further information. We request that you provide a dataset, as outlined, which includes requested data for each pivotal study submitted in your application.

Attachment 1

Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

INTRODUCTION

The purpose of this pilot for electronic submission of a single new clinical site dataset is to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process in support of the evaluation of data integrity.

DESCRIPTION OF THE SUMMARY LEVEL CLINICAL SITE DATASET

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection to facilitate the evaluation of the application. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

Site-Specific Efficacy Results

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Standard Deviation (TRTEFFS) – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS) – the standard deviation of the site-specific efficacy effect size (SITEEFFE)
- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.
- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report.

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, “TRTEFFR.”

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.
- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the “endpoint” plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1: *Table 1 Clinical Site Data Elements Summary Listing (DE)*. A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (*.xpt).

Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter "1".	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., <u>not limited to</u> only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., <u>not limited to</u> only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount (\$USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount (\$USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parities. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	MINITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)

STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLDISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Washington	George
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Washington	George
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Lincoln	Abraham

MINITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

Attachment 2

Technical Instructions:

Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clnsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

Attachment 3: Clinical Pharmacology Review Template:



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

/s/

RUSSELL G KATZ

04/09/2012