CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212028Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

×Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 212028
Assessment #01

Drug Product Name	Lemborexant
Dosage Form	Tablets
Strength	5 mg, 10 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Eisai Inc.
US agent, if applicable	n/a

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original	27-DEC-2018	All
Amendment	22-MAR-2019	Labeling
Amendment	28-MAY-2019	Manufacturing, Biopharm
Amendment	03-JUN-2019	Biopharm
Amendment	17-JUL-2019	Labeling

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Gaetan Ladouceur	Suong Tran
Drug Product	Dan Berger	Wendy Wilson-Lee
Manufacturing	Chunsheng Cai	Pei-I Chu
Biopharmaceutics	Qi Zhang	Ta-Chen Wu
Regulatory Business Process Manager	Teshara Bouie	
Application Technical Lead	Wendy Wilson-Lee	
Environmental	James Laurenson	Scott Furness

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

OPQ recommends approval of NDA 212028 for commercialization of lemborexant tablets, 5 mg and 10 mg. The applicant provided adequate information to ensure the identity, strength, purity, and quality of the proposed product. All facilities are in good standing.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Eisai seeks approval of lemborexant tablets for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance, (b) (4) The proposed dose is 5 mg daily with an allowance for dose increases up to 10 mg once daily if tolerated and needed for greater effect. Although not explicitly stated in the proposed indication, it is assumed that the proposed treatment will be for adults only. There are numerous treatment options for insomnia, including FDA-approved products, over the counter products, non-drug interventions, and lifestyle changes. Untreated insomnia is associated with increased risks of several medical and psychiatric conditions such as cardiovascular and neurological disorders (Spiegel, et al. 1999, Osorio, et. al., 2011). Eisai contends that lemborexant provides a "significant and sustained efficacy for both sleep onset and sleep maintenance with a favorable safety profile, which includes minimal impact on daily functioning" (Module 2.5 Table 2.5-8 Benefit-Risk Integrated Assessment).

The proposed drug product is a film-coated, immediate release tablet. OPQ provided advice on the CMC development program as part of End of Phase 2 meeting in November 2014 (preliminary agreement on regulatory starting materials). Eisai studied three different formulations in clinical studies. The tablet (b) (4) for the formulations used in Phase 2 and Phase 3 studies was the same but a different (b) (4) was used for the Phase 3 studies. (b) (4)

B. Quality Assessment Overview

Drug Substance: Lemborexant drug substance is a new molecular entity with a molecular formula of $C_{22}H_{20}F_2N_4O_2$ and a molecular weight of 410.42 Daltons. It is a white to off-white crystalline powder (b) (4) It contains 2 chiral centers (quaternary and tertiary carbon atoms of the cyclopropyl ring) and has a melting point between 176°C to 177°C. It is non-hygroscopic and only one crystalline form was observed by XRPD analysis. The drug substance is manufactured (b) (4) (b) (4). The specified impurity (b) (4) and unspecified impurities are adequately controlled in the drug substance specification. All the genotoxic or potentially genotoxic impurities are adequately controlled (b) (4). Therefore, no specific control is included in the drug substance specification for potential or known genotoxic

impurities. The drug substance is placed in a [redacted] The retest period is [redacted] when stored [redacted] in the proposed container closure system.

Drug Product: Lemborexant tablets are available at two strengths - 5 mg and 10 mg, to be dosed at up to 10 mg daily orally. All excipients are compendial, present in safe quantities and BSE/TSE free. The commercial formulation includes debossment and color differences that adequately distinguish the tablet strengths. Although the commercial tablet [redacted] differs from the phase 3 clinical tablets, the minor differences [redacted] do not affect quality or stability of the tablets. The specifications are adequate to ensure drug product quality and drug product batches meet specified acceptance criteria. The key analytical methods are the HPLC method used to assess identification, assay, impurities, and uniformity of dosage units. No degradation products have been identified at release or on stability.

Drug product packaging consists of an HDPE bottle enclosed with a [redacted] closure, and [redacted] seal. The primary packaging and bulk packaging components that contact the drug product are suitable for pharmaceutical or food contact per 21 CFR regulations. Registration drug product batches meet all acceptance criteria on release and during long-term and accelerated stability studies, with no significant changes or increases in degradants. Lemborexant tablets meet specifications after exposure to intense UV and visible light per prescribed Q1B ICH conditions, as well as temperatures from -20°C to 50°C for 2 weeks and 40°C for 6 months when stored in bulk packaging. The overall stability data submitted provides adequate support for a shelf-life of 24 months at USP Controlled Room Temperature.

As the Applicant has calculated that the active moiety will be introduced into the aquatic environment in quantities significantly below 1 ppb, the claim of categorical exclusion under 21 CFR 25.31 (b) is acceptable. Additionally, no extraordinary circumstances are anticipated that would trigger an environmental assessment under 21 CFR § 25.21 (a).

Labeling: All labeling deficiencies have been addressed. The Applicant has made recommended edits to the container label in response to an Information Request sent by the Agency. The Prescribing Information and labels comply with all regulatory requirements from a CMC perspective.

Manufacturing: Manufacturing process includes [redacted]. The process development was properly done in studying the operating ranges in individual unit operations, and the registration batches showed acceptable test result. The necessary IPCs are proposed [redacted]. Microbiological control is acceptable by controlling [redacted] and testing the final product in the release and stability. However, we would like them to clearly specify [redacted] the excipient low-substituted hydroxypropyl cellulose (LHPC), and provide more information [redacted]. After one round of information request, the deficiencies are resolved. The process is adequate. Facilities are acceptable based on their previous history.

Biopharmaceutics: The Biopharmaceutics review focused on 1) the evaluation of the adequacy of the proposed dissolution method and acceptance criterion, and 2) bridging throughout product development. The proposed dissolution method [900 ml of 0.1 N HCl using USP Apparatus 2 (paddle) at 50 rpm] and acceptance criterion [NLT [redacted]% (Q) in 15 minutes] for

the proposed drug product batch release and stability testing, are acceptable, based on the totality of the information and data provided (e.g., comparative dissolution profile data generated in 500 mL and 900 mL, as well as pH-dependent solubility and very rapid dissolution).

The drug product used in the Phase 3 clinical studies is reported to be the same as the proposed commercial drug product, except for the tablet color for the 5 mg strength tablet. The provided complete dissolution data support the tablet color change between the clinical and registration stability batches. The manufacturing site of the drug product batches used in the clinical and registration-stability studies is the proposed commercial site. The product bridging is adequate.

C. Risk Assessment

Assessment				
Critical Quality Attribute	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations**
Assay	Low	-	Acceptable	-
Physical Stability	Medium	Controlled by manufacturing process	Acceptable	-
Content Uniformity	Medium	Process controls and end product testing	Acceptable	-
Microbial Limits	Low	-	Acceptable	-
Dissolution	Medium	Suitable method developed	Acceptable	-
Particle Size	Low	-	Acceptable	-

Application Technical Lead Name and Date: Wendy Wilson-Lee 16AUG2019

U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Assessment Date	Comments
(b) (4)	III	(b) (4)		n/a	n/a	Sufficient information in NDA
	III			n/a	n/a	
	III			n/a	n/a	
	III			n/a	n/a	
	III			n/a	n/a	
	IV			n/a	n/a	

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	111871	Treatment of insomnia
IND	(b) (4)	

2. CONSULTS

None.

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate

Section 11 has been edited to add alphabetized excipients, and Section 16 has been edited to add corrected language for USP storage conditions. With these edits, the prescribing information meets all regulatory requirements from a CMC perspective.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Dayvigo	Adequate
Established name(s)	Lemborexant	Adequate
Route(s) of administration	Oral	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	5 mg, 10 mg	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	NA	NA

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	NA	NA

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Tablets	Adequate
Strength(s) in metric system	5 mg, 10 mg	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	NA	NA
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Pale yellow (5 mg) or orange (10mg) round, biconvex, film-coated tablets debossed with "5" or "10" and "LЄM".	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	NA	NA

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Dayvigo, lemborexant	Adequate
Dosage form(s) and route(s) of administration	5 mg and 10 mg tablets, oral administration	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	NA	NA
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Hydroxypropyl cellulose, lactose monohydrate, low-substituted hydroxypropyl cellulose, magnesium stearate. Film coating: hypromellose 2910, PEG 8000, talc, titanium dioxide, ferric oxide yellow or red	Adequate, with edits to alphabetize the inactive ingredients
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Statement of being sterile (if applicable)	NA	NA
Pharmacological/ Therapeutic class	orexin receptor antagonists	Adequate
Chemical name, structural formula, molecular weight	(1R,2S)-2-{[(2,4-dimethyl-pyrimidin-5-yl)oxy]methyl}-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide, $C_{22}H_{20}F_2N_4O_2$, 410.42	Adequate
If radioactive, statement of important nuclear characteristics.	NA	NA

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
Other important chemical or physical properties (such as pKa or pH)	Practically insoluble in water.	Adequate
For oral prescription drug products, include gluten statement if applicable	NA	NA
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	NA	NA

1.2.3 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	tablets	Adequate
Strength(s) in metric system	5 mg and 10 mg	Adequate
Available units (e.g., bottles of 100 tablets)	Bottles of 30 and 90	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Shape, color, debossing	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	NA	NA

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	NA	NA
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	NA	NA
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 20 °C to 25 °C (68 °F to 77 °F), excursions permitted between 15 °C and 30 °C (59 °F and 86 °F)	Adequate, with edits made to state USP controlled room temperature conditions.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	NA	NA
Include information about child-resistant packaging	Dispense in a tight container as defined in USP, with a child-resistant closure (as required).	Adequate

1.2.4 Other Sections of Labeling

No other sections of the labeling contain product quality information.

1.2.5 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured and Marketed by: Eisai Inc. Woodcliff Lake, NJ 07677	Adequate

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): NA

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

3.2 Carton Labeling: *NA*

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Dayvigo, lemborexant	Adequate
Dosage strength	5 mg, 10 mg	Adequate
Route of administration	Oral	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	NA	NA
Net contents (e.g. tablet count)	30 or 90 tablets	Adequate
"Rx only" displayed on the principal display	Present	Adequate
NDC number	62856-405-30, 62856-405-90, 62856-410-30, 62856-410-90	Adequate
Lot number and expiration date	Present	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 20 °C to 25 °C (68 °F to 77 °F), excursions permitted to 15 °C and 30 °C (59 °F and 86 °F)	Adequate, following edit to USP controlled room temperature conditions language.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	NA	NA
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Bar code	Present	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Distributed by Eisai Inc.	Adequate
Medication Guide (if applicable)	NA	NA
No text on Ferrule and Cap overseal	NA	NA
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	NA	NA
And others, if space is available		

Assessment of Carton and Container Labeling: *Adequate*

The labels are acceptable following edits made in response to a recommendation to revise the storage condition statement to be consistent with USP controlled room temperature. The labels comply with all regulatory requirements from a CMC perspective.

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

All labeling deficiencies have been addressed. The Applicant has made recommended edits to the container label in response to an Information Request sent by the Agency. The Prescribing Information and labels comply with all regulatory requirements from a CMC perspective.

Primary Labeling Assessor Name and Date:

Dan Berger August 1, 2019

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Wendy Wilson-Lee August 1, 2019

Dan Berger

Digitally signed by Dan Berger
Date: 8/01/2019 03:34:52PM
GUID: 56e6e1b5001a2fedae663c62a5ce7513

Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 8/01/2019 04:22:09PM
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NDA: 212028
Submission Type: 505(b)(1) NME
Drug Product Name/Strength: DAYVIGO™ (lemborexant) tablets, 5 mg, and 10 mg
Applicant Name: Eisai Inc.
Route of Administration: Oral; recommended dose is 5 mg once per night, or up to 10 mg daily.
Dosage Form: Immediate Release Film Coated Tablets
Intended for Use: For the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance, (b) (4)
Cross Referenced Applications: IND 111871 (treatment of insomnia; sleep onset and or maintenance) (b) (4)
Primary Reviewer: Qi Zhang, Ph.D.
Secondary Reviewer: Ta-Chen Wu, Ph.D.

REVIEW SUMMARY

The Biopharmaceutics review focused on **1)** the evaluation of the adequacy of the proposed dissolution method and acceptance criterion, and **2)** bridging throughout product development.

1) ***Dissolution Method and Acceptance Criterion:*** The proposed dissolution method [*900 ml of 0.1 N HCl using USP Apparatus 2 (paddle) at 50 rpm*] and acceptance criterion [*NLT (b) (4) % (Q) in 15 minutes*] for the proposed drug product batch release and stability testing, are deemed acceptable, based on the totality of the information and data provided (e.g., comparative dissolution profile data generated in 500 mL and 900 mL, as well as pH-dependent solubility and very rapid dissolution).

2) ***Bridging Throughout Product Development:*** The drug product used in the Phase 3 clinical studies is reported to be the same as the proposed commercial drug product, except for the tablet color for the 5 mg strength tablet. The provided complete dissolution data support the tablet color change between the clinical and registration stability batches. The manufacturing site of the drug product batches used in the clinical and registration-stability studies is the proposed commercial site. The product bridging is deemed adequate.

RECOMMENDATION

From the Biopharmaceutics perspective, NDA 212028 for DAYVIGO™ (lemborexant) Tablets, 5 mg, and 10 mg, is recommended for **APPROVAL**.

BIOPHARMACEUTICS ASSESSMENT

LIST of SUBMISSIONS BEING REVIEWED

eCTD # (SND #)	Received date	Document
0000 (1)	12/27/2018	Original submission
0019 (21)	05/28/2019	Response to Information Request dated 05/14/2019
0023 (25)	06/03/2019	Response to Information Request dated 05/14/2019
	07/30/2019	Response via email to Information Request dated 07/26/2019

DRUG SUBSTANCE

Biopharmaceutics Considerations

Lemborexant	
NTI drug	Unknown
BCS solubility reported by the Applicant	Low and pH dependent; highly soluble at pH 1 (0.1 N HCl) [*1.6 mg/mL vs. 0.04 mg/mL (10 mg/250 mL)*], but practically insoluble from pH 3.0 to pH 6.8 (0.0148 to 0.025 mg/mL). **Dissolution Media** / **Solubility at 37 °C (µg/mL)** / **Volume of Dissolution Media Which Meet Sink Condition [a] for 10 mg Strength** 0.1 mol/L hydrochloric acid: 1606.8: 19 mL Diluted McIlvaine buffer (pH 3.0): 25.0: 1200 mL USP acetate buffer (pH 4.5): 16.9: 1775 mL USP phosphate buffer (pH 6.8): 14.8: 2027 mL a: Volume of medium (b) (4) required in order to form a saturated solution of drug substance.
BCS permeability reported by the Applicant	Not reported. The human mass balance study (E2006-A001-007) showed that the mean cumulative recovery of administered radioactivity was 57.4% in feces and 29.1% in urine. The percent of lemborexant excreted unchanged in the urine is negligible (<1% dose).
BCS class reported by Applicant	Not reported.
BCS Designation	Not submitted nor required.
Particle size	d (0.9): NMT (b) (4) µm; See the Section "Drug Substance Particle Size Impact on Dissolution"
Polymorphism	Only one crystalline form identified by XRD. No other polymorphs have been observed per the Applicant.
Is Cmax critical?	Refer to Clinical and Clinical Pharmacology Reviews.
Is Tmax critical?	No; Tmax = 1-3 hours; " (b) (4) , time to sleep

	onset may be delayed if taken with or soon after a meal", per the proposed labeling.

DRUG PRODUCT

Lemborexant tablets are pale yellow (5 mg) or orange (10 mg), film-coated, biconvex shaped, debossed, and unscored tablets. The manufacturing process of lemborexant tablets consists of (b) (4)

(b) (4)

DISSOLUTION

- **Proposed Dissolution Method and Acceptance Criterion:**

USP Apparatus	Speed (RPM)	Medium	Volume/Temp	Acceptance Criterion
II	50	0.1 N HCl	900 mL/37°C	NLT (b) (4)% (Q) at 15 minutes

- **Dissolution Method Development:**

(b) (4)

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(b) (4)

- ***Discriminating Capability of the Dissolution Method:***

The Applicant showed the discriminatory ability of the dissolution method against changes in formulation (b) (4) process variables (b) (4) and storage (b) (4)

Manufacturing: Lemborexant shows characteristics of (b) (4) of lemborexant for achieving desirable dissolution. The Applicant showed that the proposed dissolution method can differentiate between 10 mg (b) (4) tablets manufactured using (b) (4) sample or using nominal (b) (4) vs. overage (b) (4) amount of (b) (4) (Figures 3 and 4). The proposed dissolution method is also shown to discriminate the batches manufactured using the (b) (4) sample not aged and under stress condition (Figure 4).

Formulation: The Applicant showed that the proposed dissolution method can reject the batch manufactured using overage amounts of (b) (4)%, nominal condition: (b) (4)%) (Figure 5).

The proposed QC dissolution method is expected to be lacking in discriminating power toward particle size of drug substance (Figure 6), small or meaningful (< (b) (4)%) changes in formulation compositions, and CPPs, due to the very high solubility of the drug substance and very rapid dissolution of the drug product in the proposed QC dissolution medium.

Figure 3: Dissolution Profiles of (b) (4) Samples and Drug Substance for 10 mg (b) (4) Tablets

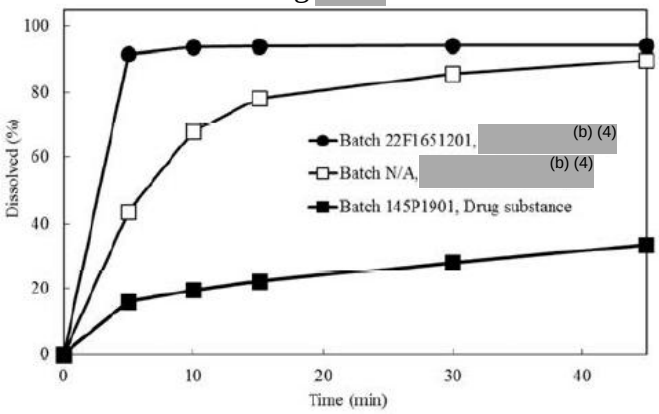


Figure 4: Dissolution Profiles of Lemborexant 10 mg (b) (4) Tablets Manufactured Using Nominal (b) (4) and Overage (b) (4)

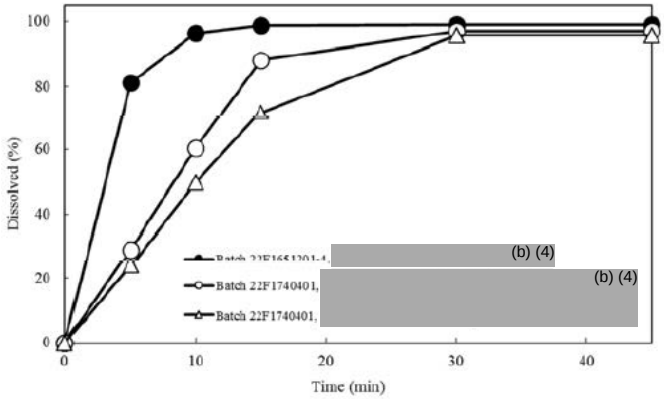
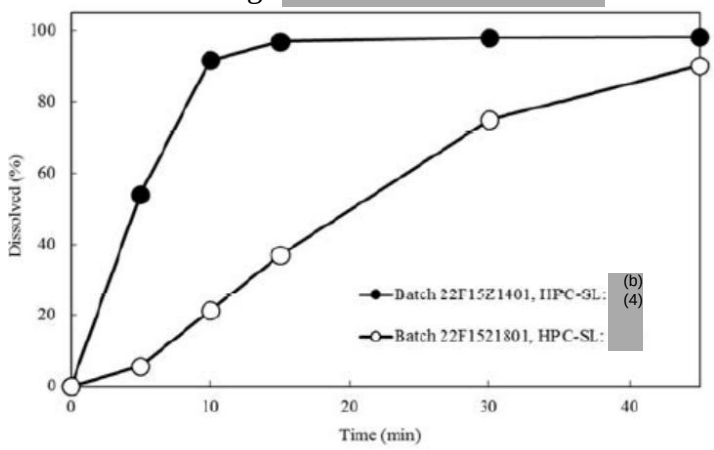


Figure 5: Dissolution Profiles of Lemborexant 10 mg (b) (4) Tablets Manufactured Using Nominal (b) (4) and Overage (b) (4)



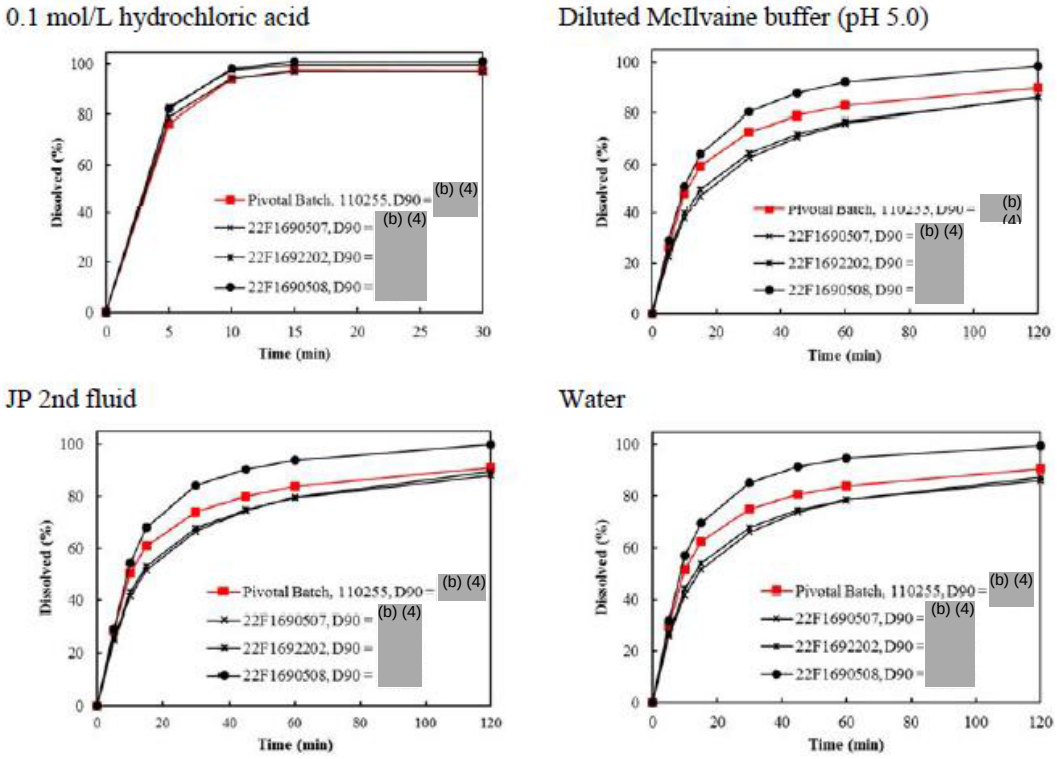
- ***Impact of Drug Substance Particle Size on Dissolution***

The proposed acceptance criterion for the drug substance particle size is D_{90}: NMT (b) (4) µm. However, the drug substance batches used for clinical studies have D_{90} values between (b) (4) µm, and between (b) (4) µm used for registration/stability batches (3.2.S.4.5: Table 3.2.S.4.5-9).

From a Biopharmaceutics perspective, lemborexant is considered to be a BCS Class II/IV drug with low and pH-dependent solubility, the particle size of lemborexant beyond those of the clinical batches could have an impact on dissolution. Thus, the risk is high. The Applicant showed that Lemborexant 2.5 and 10 mg core tablets manufactured with the (b) (4) µm drug substance had no impact on the dissolution profile of lemborexant by using the proposed QC dissolution method (Sec. 3.2.P.2.1 Figures 3.2.P.2.1-1 and 3.2.P.2.1-2). The Applicant was requested to provide additional multimedia dissolution data in water, and two other buffer media at pH 4.5 and pH 6.8 to support the proposed particle size range of NMT (b) (4) um.

Based on the dissolution data provided in the Applicant's 5/28/2019 Response, though the dissolution in water and pH 4.5 and pH 6.8 media was shown slower for the 10 mg (b) (4) tablets containing the (b) (4) µm drug substance, compared to the pivotal clinical batch containing the smaller (b) (4) µm API particle size, the dissolution profiles are considered similar (f_2 > 50) (Figure 6). This Reviewer concluded that, the difference (within (b) (4)%) between dissolution profiles is unlikely to impact in vivo performance, based on risk-assessment for the proposed drug product (e.g., very rapid dissolution in 0.1 N HCl, and Tmax is not critical).

Figure 6: Comparative Dissolution Profiles of Lemborexant 10 mg (b) (4) Tablets Having Particle Sizes Ranging from (b) (4) µm in Various Dissolution Media Against Pivotal Batch of Lemborexant 10 mg Core Tablets (D90 = (b) (4) µm)



- ***Dissolution Acceptance Criterion:***

The proposed dissolution acceptance criterion is "Q= (b) (4)% at 15 minutes". Complete in vitro dissolution profiles for the pivotal clinical batch and registration stability batches demonstrate the very rapid and complete dissolution of the drug product using the proposed QC dissolution method (Figures 1 and 2).

- ***Validation for Dissolution Method:***

The robustness of the proposed dissolution method with respect to dissolution testing conditions was not determined, which, in this Reviewer's view, would not be a concern since variability as a result of slight variation in dissolution conditions (e.g., agitation speed, medium temperature) would not be expected to have a significant impact on resulting dissolution profiles due to the very rapid dissolution. Refer to the

Drug Product Review for the evaluation of the adequacy of the validation of the analytical UV method (including the UV method used for dissolution testing).

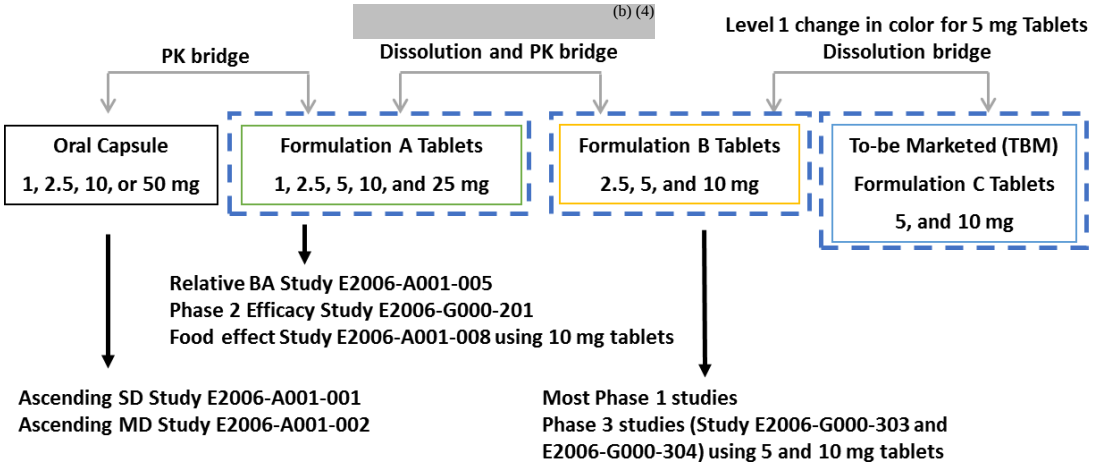
Reviewer's Overall Assessment: **ADEQUATE**

The proposed dissolution method and acceptance criterion are acceptable for the quality control based on the availability of sufficient sink condition and complete, very rapid dissolution, as well as discriminating ability of the method against changes in formulation (b) (4) *and manufacturing process* (b) (4). *The provided stability data for 6-month accelerate, and 12-month long-term conditions show that all exhibit batches passed dissolution for the recommended dissolution acceptance criterion at Stage 1. There is no significant trend observed for dissolution on stability.*

BRIDGING THROUGHOUT PRODUCT DEVELOPMENT

A total of four oral formulations of Lemborexant (capsule, Formulation A and B film coated tablets, and proposed commercial or Formulation C tablets) were developed during drug product development. The product bridging among the four formulations is illustrated in Figure 7.

Figure 7: Schematic Diagram of Formulations Used in Clinical Development and Product Bridging



Relative BA study (Study E2006-A001-005) were conducted for capsule vs. Formulation A at a 2.5, 10 and 25 mg dose. Formulations A and B are the same except (b) (4) for color change (b) (4). The Applicant demonstrated the similarity via comparative in vitro dissolution profiles between Formulation A and B for the same dosage strengths (2.5 mg, 5 mg and 10 mg vs. 2.5 mg, 5 mg and 10 mg) using the dissolution media at pH 1.2, pH 5, pH 6.8, and water. In addition, the provided PK, efficacy and safety data support comparability between these two formulations; refer to the Clinical Pharmacology and Clinical Reviews.

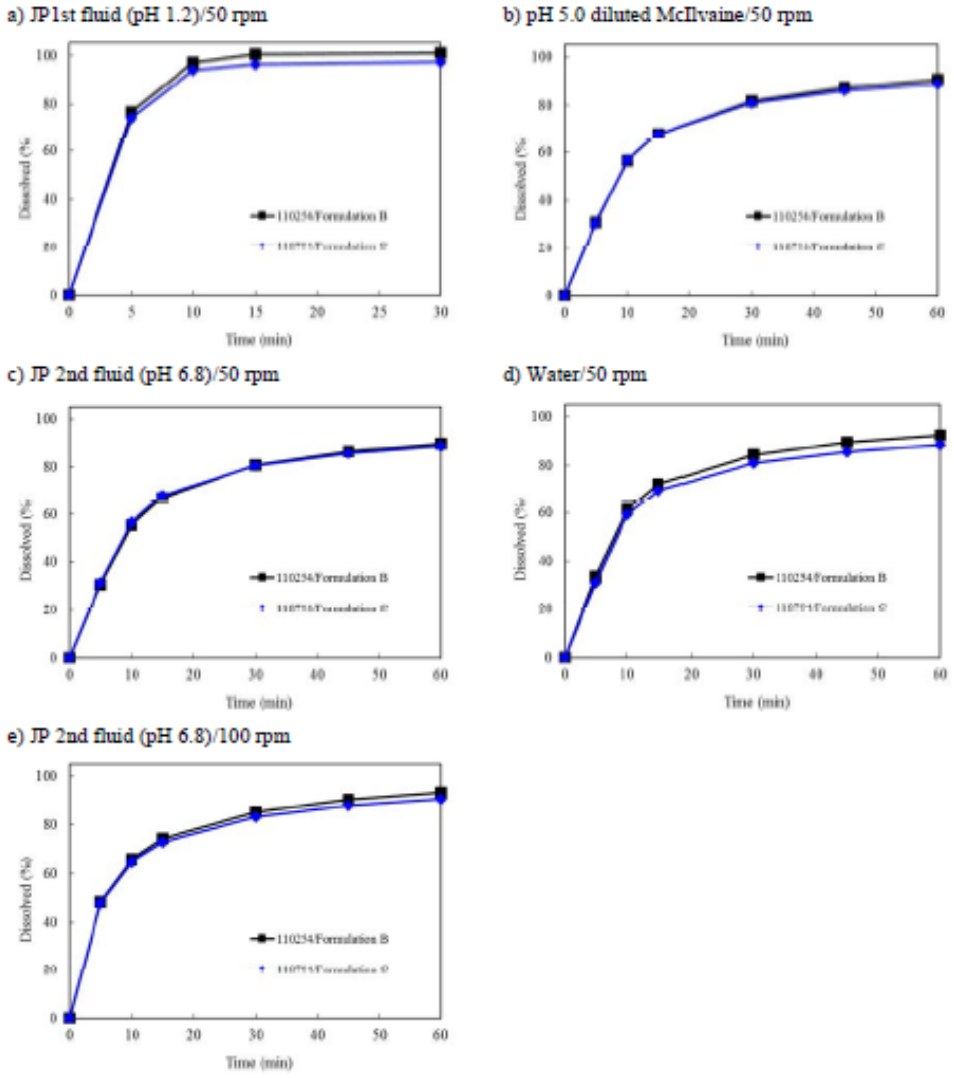
(b) (4)

(b) (4) The Applicant provided comparative dissolution profiles data to bridge different strengths of Formulation B. Dissolution

of all strengths reaches (b) (4)% at pH 1.2, and the dissolution profiles at pH 5, and pH 6.8, and water were comparable ($f_2 > 50$).

The proposed commercial drug product formulation (Formulation C) is the same as Formulation B used in most Phase 1 and pivotal Phase 3 clinical studies, except for the difference in tablet color for the 5 mg strength (Level 1 change) in order to distinguish it from the 10 mg strength. The Applicant provided comparable dissolution profiles between Formulation B (Phase 3 clinical batch) and Formulation C for the 5 mg strength, performed in water and dissolution media at pH 1, pH 5, and pH 6.8 (Figure 8). In addition, complete dissolution data using the proposed QC dissolution method demonstrate that the dissolution rates were not influenced by the color change between the pivotal clinical and registration-stability b_ches for the 5 mg strength (Figures 1 and 2; f_2 calculation is not required as the dissolution reached > (b) (4)% in 15 minute).

Figure 8 (3.2.P.2.2-7): Dissolution Profiles of Tablet Formulation B and Tablet Formulation C of Lemborexant 5 mg Tablets in Various Dissolution Media



Reviewer's Overall Assessment: ADEQUATE

The formulation of the drug product used in the Phase 3 clinical study is reported to be the same as the proposed commercial drug product, except for the tablet color for the 5 mg strength. The provided complete dissolution data support the color change between the pivotal clinical and registration-stability batches. The drug product batches used in the clinical and registration-stability studies were manufactured at the proposed commercial site.

BIOWAIVER REQUEST

A biowaiver is not requested nor required. The Applicant conducted the clinical studies using both 5 mg and 10 mg strengths.

Qi Zhang

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Date: 8/12/2019 10:51:08PM
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Ta-Chen Wu

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WENDY I WILSON-LEE
08/16/2019 09:58:49 AM