

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**211280Orig1s000**

**PRODUCT QUALITY REVIEW(S)**

**Recommendation: APPROVAL**

**NDA 211280  
Review #01**

|                         |                       |
|-------------------------|-----------------------|
| Drug Name/Dosage Form   | Lasmitidan Tablets    |
| Strength                | 50 mg, 100 mg         |
| Route of Administration | Oral                  |
| Rx/OTC Dispensed        | Rx                    |
| Applicant               | Eli Lilly and Company |
| US agent, if applicable | n/a                   |

| SUBMISSION(S) REVIEWED   | DOCUMENT DATE | SUBMISSION(S) REVIEWED   | DOCUMENT DATE |
|--------------------------|---------------|--------------------------|---------------|
| <i>Original (SD 1)</i>   | 11-OCT-2018   | <i>Amendment (SD 28)</i> | 16-MAY-2019   |
| <i>Amendment (SD 6)</i>  | 27-NOV-2018   | <i>Amendment (SD 31)</i> | 30-MAY-2019   |
| <i>Amendment (SD 12)</i> | 02-JAN-2019   | <i>Amendment (SD 37)</i> | 17-JUN-2019   |
| <i>Amendment (SD 20)</i> | 26-MAR-2019   | <i>Amendment (SD 39)</i> | 21-JUN-2019   |
| <i>Amendment (SD 25)</i> | 05-APR-2019   | <i>Amendment (SD 40)</i> | 05-JUL-2019   |
| <i>Amendment (SD 26)</i> | 30-APR-2019   |                          |               |

**Quality Review Team**

| DISCIPLINE                          | PRIMARY REVIEWER | SECONDARY REVIEWER                                        | OPQ OFFICE |
|-------------------------------------|------------------|-----------------------------------------------------------|------------|
| Drug Substance                      | Charles Jewell   |                                                           | ONDP       |
| Drug Product                        | Dan Berger       | Wendy Wilson-Lee                                          |            |
| Labeling                            |                  |                                                           |            |
| Environmental                       | Raanan Bloom     | Scott Furness                                             | OPF        |
| Manufacturing                       | Qin Liang        | Nallaperumal Chidambaram (Process)/Vidya Pai (Facilities) |            |
| Biopharmaceutics                    | Yang Zhao        | Ta-Chen Wu                                                | ONDP       |
| Regulatory Business Process Manager | Dahlia Walters   |                                                           | OPRO       |
| Application Technical Lead          | Wendy Wilson-Lee |                                                           | ONDP       |

## Quality Review Data Sheet

### 1. RELATED/SUPPORTING DOCUMENTS

#### A. DMFs:

| DMF #   | Type     | Holder | Item Referenced | Status | Review Date | Comments                               |
|---------|----------|--------|-----------------|--------|-------------|----------------------------------------|
| (b) (4) | Type III |        | (b) (4)         | n/a    | n/a         | Sufficient information included in NDA |
|         | Type III |        |                 | n/a    | n/a         | Sufficient information included in NDA |

#### B. Other Documents: *IND, RLD, or sister applications*

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION                         |
|----------|--------------------|-------------------------------------|
| IND      | 103420             | LY573144 for treatment of migraines |
|          |                    |                                     |

### 2. CONSULTS

None.

## Executive Summary

### I. Recommendations and Conclusion on Approvability

**OPQ recommends approval NDA 211280 from a quality perspective.** The Office of Pharmaceutical Quality Review team has assessed the NDA with respect to Chemistry, Manufacturing, and Controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports.

### II. Summary of Quality Assessments

#### A. Product Overview

Eli Lilly developed lasmitidan tablets for the acute treatment of migraines with and without aura in adults. The applicant contends that the product has an improved safety profile compared to standard triptan-based therapies due to the lack of vasoconstrictive effects. The applicant proposed a Schedule V controlled substance listing based on the findings of low abuse potential in their assessments. The product is not an abuse deterrent formulation.

OPQ provided guidance during development as part of several meetings and correspondences (Pre-NDA Meeting August 2018, Type C Written Responses Only October 2015, CMC Only Type C Written Responses August 2017, BCS Designation Advice Letter August 2018). Issues discussed included information required to support in-vitro bridging of formulation, method development for specified impurities, polymorphism control strategy, tablet strength differentiation strategy, drug product registration stability data package, and BCS designation for the product.

The applicant identified description, identification, potency, purity, content uniformity, and drug release as critical quality attributes for this product. The initial risk assessment identified solid state properties as a moderate risk. The drug substance can exist in multiple polymorphic forms (b) (4)

(b) (4). Comparability of performance of the different polymorphs, control of polymorphism during the manufacturing, and confirmation of polymorphic form over the proposed shelf-life were key review issues.

Although not identified as a high or moderate risk, the applicant proposed disintegration in lieu of dissolution testing at release and on stability. (b) (4)

(b) (4). The proposed control strategy relies on disintegration testing to ensure that drug release is achieved over the product shelf-life. Suitability and acceptability of this approach to ensure drug release was a key review issue.

The applicant employed an enhanced, quality by design, development approach for the product. Numerous design of experiments were conducted to establish a proposed drug

product manufacturing design space to mitigate risks during manufacturing and to establish the in-process control parameters and acceptance criteria but is not intended to be used for regulatory flexibility.

|                                                                     |                                                                                       |
|---------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| <b>Proposed Indication(s) including Intended Patient Population</b> | <b><i>Acute treatment of migraines with and without aura in adults (proposed)</i></b> |
| <b>Duration of Treatment</b>                                        | <b><i>Episodic</i></b>                                                                |
| <b>Maximum Daily Dose</b>                                           | <b><i>200 mg (proposed)</i></b>                                                       |

**B. Quality Assessment Overview**

The drug substance is referred to by the International Nonproprietary Name, Lasmiditan hemisuccinate. The USAN nomenclature for the same compound is Lasmiditan succinate. The most important drug substance attribute for drug product manufacture is the (b) (4) particle size. The proposed control has acceptable compatibility for (b) (4) (b) (4) drug product manufacture. The particle size distribution is not a critical quality attribute so only an (b) (4) limit is specified.

The drug substance is manufactured using a cGMP process (b) (4) (b) (4). The regulatory starting materials were agreed to by the FDA earlier in development. It should be noted that no impurities originating in the three starting materials impact the impurity profile of the drug substance according to criteria discussed in the ICH Q11 Q&A Guideline for the selection of starting materials. (b) (4) (b) (4). There are two critical process steps in the synthesis. (b) (4) (b) (4). All other steps are controlled (b) (4) (b) (4) to proven acceptable ranges (PARs). A full process development section was provided describing how these PARs were determined.

Impurities (b) (4) are demonstrated purged in the commercial process, therefore, there are no specified impurities in the release specification, and all unspecified impurities are limited to NMT (b) (4)%. A risk assessment of mutagenic and carcinogenic impurities per ICH M7 was performed and the combination of empirical purge data and calculated purge based on scientific understanding demonstrates all potential mutagenic and carcinogenic impurities are purged to less than (b) (4)% their acceptable intake based on the labeled maximum dose for this drug substance. The control of mutagenic impurities is performed (b) (4) (b) (4) with limits (b) (4) for critical mutagenic impurities demonstrated to purge (b) (4).

(b) (4) is the desired polymorphic form for the drug substance. The information provided adequately demonstrated that the drug substance manufacturing process

(b) (4) is stable as demonstrated by drug substance stability studies, in the recommended storage container closure system, and storage conditions between (b) (4). **Stability data supports a retest period of (b) (4) months for the drug substance.**

**The drug product is of adequate quality, with minimal risks to patients identified.**

The drug product consists of lasmiditan hemisuccinate tablets at two strengths – 50 mg and 100 mg free base to be dosed at up to 200 mg orally in a 24-hour period. These are readily distinguishable by color and debossing. All excipients are compendial, present in acceptable quantities at the maximum dose and BSE/TSE free. (b) (4)

(b) (4)

The specifications are adequate to ensure drug product quality and drug product batches meet specified acceptance criteria. The key analytical method is an HPLC method used to assess assay, uniformity of dosage units, and degradation products, which is adequately validated. Related impurities, elemental impurities and residual solvents are adequately controlled to minimize risks to patient safety. Commercial packaging consists of (b) (4) blisters, sealed with (b) (4) materials which are suitable for pharmaceutical or food contact per 21 CFR regulations.

Registration batches meet all acceptance criteria on release and during long-term and accelerated stability studies, with no significant changes or increases in degradants

(b) (4)

(b) (4). The drug product continues to meet specifications after exposure to stress conditions and intense UV/visible light per Q1B ICH conditions. **The overall stability data submitted provides adequate support for a shelf-life of 24 months at USP Controlled Room Temperature.**

The proposed commercial manufacturing of Lasmiditan tablet, 50 mg and 100 mg includes (b) (4) (b) (4). The commercial scale batch size will be within 10 X limit of that of exhibit batches. The equipment, process parameters, as well as specification limits have been included in the master batch record.

At the time of Information Request #1, the concerns for the intended commercial manufacturing are related to the following: (b) (4) (b) (4). In responses to multiple information requests, the applicant provided (b) (4) (b) (4) the data to support the proposed (b) (4). **Following a review of the application and inspectional documents, there are no**

**significant, outstanding manufacturing or facility risks for the other facilities. The manufacturing facilities for NDA 211280 are found to be acceptable.**

The biopharmaceuticals review evaluated the adequacy of (1) the proposed disintegration testing in lieu of a dissolution testing for quality control testing of the drug product, (2) bridging of clinical and commercial formulations, and (3) bridging of formulations manufactured at different sites.

In lieu of dissolution testing for routine quality control purposes, the applicant proposed disintegration testing [water as the medium, with disks] as the regulatory in-vitro method for drug product release. The proposed disintegration testing and disintegration acceptance criterion [NMT (b) (4)] is acceptable. (b) (4)

(b) (4)  
(b) (4). The discriminating ability of the dissolution method could not be demonstrated because of the very rapid drug release.

The applicant established the bridge between the T2 (commercial) and T1 (clinical and registration stability) products with comparative dissolution profile data generated in multi-pH media. The bridging between commercial and clinical drug product formulations is acceptable. The applicant established the bridge between the product manufacturing sites with comparative dissolution profile data generated using the proposed dissolution method. The bridging between manufacturing sites is acceptable.

**The Prescribing Information and labels comply with all regulatory requirements from a CMC perspective.**

**The applicant's claim of categorical exclusion under 21 CFR 25.31(b) and provided statement of no extraordinary circumstance are acceptable.** Modeled and available information indicates a low potential for lasmiditan interaction with estrogen and androgen receptors. Modeled aquatic toxicity results show a large margin between exposure and effects. The Fish Plasma Model output indicates that additional studies may be required. However, based on the expected low exposure concentrations, model results indicate a low environmental risk is expected due to approval of this application.

**C. Special Product Quality Labeling Recommendations (NDA only)**

None.

**D. Lifecycle Management Considerations**

1. (b) (4) scrutinize all process changes for impact on impurity profile (b) (4), significant control of mutagenic impurities is handled in (b) (4) specifications and based on (b) (4) (b) (4) assessments in the current process

2.

(b) (4)

3. Comparability protocol approved to support a change (b) (4) used during drug substance manufacturing (b) (4)
4. Comparability protocol approved to support a change planned for the drug product annual stability commitment to reduce the required test attributes and time points
5. Disintegration testing is used in lieu of dissolution for routine batch release and stability testing; A dissolution method is available to support required testing to support post approval changes



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Wilson- Lee

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**LABELING**

*{For NDA Only}*

**I. Package Insert**

**1. Highlights of Prescribing Information**

| Item                                                                      | Information Provided in NDA |
|---------------------------------------------------------------------------|-----------------------------|
| Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))              |                             |
| Proprietary name and established name                                     | Adequate                    |
| Dosage form, route of administration                                      | Adequate                    |
| Controlled drug substance symbol (if applicable)                          | Adequate                    |
| Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8)) |                             |
| Summary of the dosage form and strength                                   | Adequate                    |

**2. Section 2 Dosage and Administration**

| Item                                                                                                                     | Information Provided in NDA |
|--------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| (Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))                                                                 |                             |
| Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents) | NA                          |

**3. Section 3 Dosage Forms and Strengths**

| Item                                                                                                                                             | Information Provided in NDA |
|--------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| (Refer to Labeling Review Tool and                                                                                                               | 21 CFR 201.57(c)(4))        |
| Available dosage forms                                                                                                                           | Adequate                    |
| Strengths: in metric system                                                                                                                      | Adequate                    |
| Active moiety expression of strength with equivalence statement (if applicable)                                                                  | Adequate                    |
| A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable. | Adequate                    |

**4. Section 11 Description**

| Item                                                                                                                                                                                                                                                             | Information Provided in NDA                                                                             |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|
| (Refer to Labeling Review Tool and                                                                                                                                                                                                                               | 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)) |
| Proprietary name and established name                                                                                                                                                                                                                            | Adequate                                                                                                |
| Dosage form and route of administration                                                                                                                                                                                                                          | Adequate                                                                                                |
| Active moiety expression of strength with equivalence statement (if applicable)                                                                                                                                                                                  | Adequate                                                                                                |
| For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>) | Adequate                                                                                                |
| Statement of being sterile (if applicable)                                                                                                                                                                                                                       | NA                                                                                                      |
| Pharmacological/ therapeutic class                                                                                                                                                                                                                               | Adequate                                                                                                |
| Chemical name, structural formula, molecular weight                                                                                                                                                                                                              | Adequate                                                                                                |
| If radioactive, statement of important nuclear characteristics.                                                                                                                                                                                                  | NA                                                                                                      |
| Other important chemical or physical properties (such as pKa or pH)                                                                                                                                                                                              | Adequate with edits made.                                                                               |

**5. Section 16 How Supplied/Storage and Handling**

| Item                                                                                         | Information Provided in NDA |
|----------------------------------------------------------------------------------------------|-----------------------------|
| (Refer to Labeling Review Tool and                                                           | 21 CFR 201.57(c)(17))       |
| Strength of dosage form                                                                      | Adequate                    |
| Available units (e.g., bottles of 100 tablets)                                               | Adequate                    |
| Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number | Adequate                    |
| Special handling (e.g., protect from light)                                                  | NA                          |
| Storage conditions                                                                           | Adequate with edits made    |
| Manufacturer/distributor name (21 CFR 201.1(h)(5))                                           | Adequate                    |

**Reviewer’s Assessment of Package Insert: *Adequate***

Section 11 was edited to add physical/chemical properties, and section 16 was edited to add the temperature scale designation after each number. With these edits, the prescribing information meets all regulatory requirements from a CMC perspective.

**II. Labels:**

**1. *Container and Carton Labels***

Blister Pack (100 mg strength):

(b) (4)



**2. Carton Label**



| Item                                                                               | Information provided in the container (blister) label | Information provided in the carton label(s) |
|------------------------------------------------------------------------------------|-------------------------------------------------------|---------------------------------------------|
| Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2)) | Adequate                                              | Adequate                                    |
| Dosage strength                                                                    | Adequate                                              | Adequate                                    |
| Net contents                                                                       | NA for blister                                        | Adequate                                    |
| “Rx only” displayed prominently on the main panel                                  | Addressed by DMEPA                                    | Adequate                                    |
| NDC number (21 CFR 207.35(b)(3)(i))                                                | NA for blister                                        | Adequate                                    |
| Lot number and expiration date (21 CFR 201.17)                                     | Adequate                                              | Adequate                                    |
| Storage conditions                                                                 | NA for blister                                        | Adequate with DMEPA recommendations         |
| Bar code (21CFR 201.25)                                                            | Adequate                                              | Adequate                                    |
| Name of manufacturer/distributor                                                   | Adequate                                              | Adequate                                    |
| And others, if space is available                                                  |                                                       |                                             |

**Reviewer's Assessment of Labels: Adequate**

The labels comply with all regulatory requirements from a CMC perspective.

***List of Deficiencies: None******Overall Assessment and Recommendation:***

All labeling deficiencies have been addressed. The Prescribing Information and labels comply with all regulatory requirements from a CMC perspective.

***Primary Labeling Reviewer Name and Date:***

Dan Berger                      June 12, 2019

***Secondary Reviewer Name and Date (and Secondary Summary, as needed):***

Wendy Wilson                 June 12, 2019



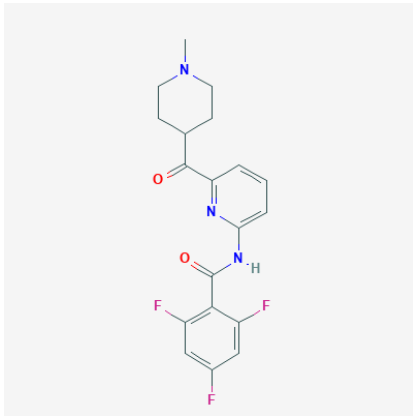
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**ENVIRONMENTAL REVIEW*****1. Regional Information******1.12.14: Environmental Analysis*****Application:** NDA 211280**Drug product:** REYVOW tablets, for oral use**API:** Lasmiditan

**Indication:** REYVOW™ is a serotonin (5-HT) 1F receptor agonist (ditan) indicated for the acute treatment of migraine with or without aura in adults.

**Claim of Categorical Exclusion:** The applicant has submitted a claim of categorical exclusion under 21 CFR 25.31(b) and a statement of no extraordinary circumstances under 21 CFR 25.21. Minimal supporting information is provided. An estimated environmental concentration is provided (see below). No environmental effects data are provided. The applicant does state in support of no extraordinary circumstances that there is no known impact upon endangered species and no estrogenic, androgenic, or thyroid activity has been observed with lasmiditan.

**Mode of action:** REYVOW is a high affinity, centrally-penetrant, selective 5-HT<sub>1F</sub> receptor agonist without significant pharmacological activity at 5-HT<sub>1B</sub> or 5-HT<sub>1D</sub> receptors. Evidence suggests that lasmiditan exerts its therapeutic effects in the treatment of migraine by decreasing neuropeptide release and inhibiting pain pathways, including the trigeminal nerve, without causing vasoconstriction in coronary arteries.

**Environmental Exposure:** The US annual peak sales volume of lasmiditan will be approximately [REDACTED] (b) (4). The total amount of API introduced into the aquatic environment (EIC) as a result of the use of this product is estimated to be less than [REDACTED] (b) (4) µg/L. The calculations do not account for API loss due to metabolism, WWTP treatment, sedimentation, environmental degradation or dilution.

**Application Review:** In review of the claim for categorical exclusion, in addition to the provided information, the following models were used:

## FISH PLASMA MODEL



Based on the fish plasma model result (ER= (b) (4)), fish chronic studies may be needed for lasmiditan (ER < (b) (4)).

## MODEL PREDICTIONS

### 1. Aquatic Toxicity predictions (Danish OSAR DB)



The EIC ( (b) (4)  $\mu\text{g/L}$ ) is at least 100-fold lower than the lowest predicted acute toxicity value (b) (4)  $\mu\text{g/L}$ ) from analogues.

### 2. ECOSAR

- QSAR predictions for acute and chronic effects
- Functional groups used in predictions: (b) (4)

#### 2.1 ACUTE TOXICITY



EIC is 8,000-fold lower than predicted acute toxicity value for most sensitive organism



## 2.2 CHRONIC TOXICITY

(b) (4)

EIC is 1,000-fold lower than predicted chronic toxicity value for most sensitive organism (b) (4)

### 3. QSARs for estrogen and androgen receptor activity:

- Predictions for Estrogen receptor activity **NOT** reported in Mansouri et al., 2016 (CERAPP)
- **INACTIVE** in binding, agonist and antagonist ER models (OCHEM model)
- **INACTIVE** in binding, agonist, antagonist AR models (OCHEM model)

#### ***Reviewer's Assessment: Adequate***

*Modeled and available information indicates a low potential for lasmiditan interaction with estrogen and androgen receptors. Modeled aquatic toxicity results show a large margin between exposure and effects. The Fish Plasma Model output indicates that additional studies may be required. However based on the expected low exposure concentrations, model results indicate a low environmental risk is expected due to approval of this application.*

*The applicant's claim of categorical exclusion under 21 CFR 25.31(b) and provided statement of no extraordinary circumstance are acceptable.*

***Primary Environmental Reviewer Name and Date: Raanan A. Bloom, Ph.D.***

***Secondary Reviewer Name and Date: Scott Furness, Ph.D.***



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## BIOPHARMACEUTICS

**NDA: 211280; 505(b)(1)**

**Drug Product Name/Strengths:** REYVOW™ (Lasmiditan) Tablets/50 mg and 100 mg

**Route of Administration:** Oral

**Applicant Name:** Eli Lilly and Co.

**Indication:** Acute treatment of migraine with or without aura in adults

**List of Reviewed Submissions:**

Original submission dated 10/11/2018

Response dated 3/26/2019 to the Information Request dated 3/12/2019

IND 103420 submission dated 3/4/2019

**Biopharmaceutics Review Team:**

Primary Reviewer: Yang Zhao, PhD

Secondary Reviewer: Ta-Chen Wu, PhD

### REVIEW SUMMARY:

**Submission:** Eli Lilly and Co. submitted NDA 211280 seeking approval for REYVOW™ (Lasmiditan) Tablets, 50 mg and 100 mg, under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for the acute treatment of migraine with or without aura in adults.

**Review Objective:** The Biopharmaceutics Review evaluated the adequacy of (1) the proposed disintegration testing in lieu of a dissolution testing, for QC testing of the proposed drug product 50 mg and 100 mg strengths, (2) bridging of clinical and commercial formulations, and (3) bridging of formulations manufactured at different sites. Key findings of the assessment are summarized below.

(1) **Disintegration Testing and Dissolution Testing:** The proposed dissolution method for REYVOW™ Tablets, 50 mg and 100 mg, is as follows: USP Apparatus 2 (paddle) at 75 rpm in 500 mL of 0.01N HCl, 37°C. Note that the dissolution testing was (b) (4) not for the quality control purpose. Discriminating ability of the dissolution method could not be demonstrated because of the very rapid drug release. Dissolution acceptance criterion is not proposed for the proposed drug product, which is substituted by a proposed disintegration testing (water as the medium, with disks) as the regulatory in-vitro method for drug product release. The proposed disintegration testing and *disintegration acceptance criterion of NMT* (b) (4) (b) (4) for the quality control in lieu of dissolution testing for REYVOW™ Tablets is acceptable.

(2) **Bridging of Different Formulations:** The Applicant established the bridge between the T2 (commercial) and T1 (clinical and registration stability) products with

comparative dissolution profile data generated in multi-pH media. The bridging between commercial and clinical drug product formulations is acceptable.

- (3) **Bridging of Formulations Manufactured at Different Sites:** The Applicant established the bridge between the product manufacturing sites of (b) (4) and Eli Lilly del Caribe with comparative dissolution profile data generated using the proposed dissolution method. The bridging between manufacturing sites is acceptable.
- (4) **BCS Class-I Designation:** The FDA granted the BCS Class-I status to REYVOW™ Tablets (Advice Letter dated 8/2/2018 in DARRTS; IND 103420) on the basis of (i) high solubility of drug substance (lasmiditan) based on the proposed highest strength/dose, (ii) high permeability of lasmiditan based on permeability data from human mass-balance study and Caco-2 cells, and (iii) very rapid dissolution ( $> \frac{(b)}{(4)}\%$  in 15 minutes) in multi-pH media.

#### **OVERALL RECOMMENDATION:**

From the Biopharmaceutics perspective, the provided information is **ADEQUATE** and NDA 211280 for REYVOW™ Tablets, 50 mg and 100 mg is recommended for **APPROVAL**.

**BIOPHARMACEUTICS ASSESSMENT**

**1. DRUG PRODUCT:**

Lasmiditan is a serotonin (5-HT) 1F receptor agonist (ditan) indicated for the acute treatment of migraine with or without aura in adults. Per Applicant’s proposed labeling, the recommended dose of REYVOW™ Tablets are 50 mg, 100 mg or 200 mg, with the maximum dose not exceeding 200 mg in 24 hours.

Lasmiditan immediate-release (IR) Tablets is available as oval 50 and 100 mg, debossed, aqueous film-coated tablets. The 50 mg tablet is a light gray, oval tablet debossed with “4312” on one side and “L-50” on the other. The 100 mg tablet is light purple, oval tablet debossed with “4491” on one side and “L-100” on the other. The tablets are manufactured by (b) (4) - (b) (4) (b) (4). The composition of REYVOW™ Tablets are as shown in Table 1 and proportional between 50 mg and 100 mg.

**Table 1. Composition of commercial REYVOW™ Tablets, 50 mg and 100 mg**

| Component                                                              | Quantity (mg/tablet) |        | Function          | Reference to Standards               |
|------------------------------------------------------------------------|----------------------|--------|-------------------|--------------------------------------|
|                                                                        | 50 mg                | 100 mg |                   |                                      |
| <b>Core Tablet</b> - (b) (4)                                           |                      |        |                   |                                      |
| Lasmiditan Hemisuccinate <sup>a</sup>                                  | 57.824               | 115.65 | Active Ingredient | In house, refer to Section 3.2.S.4.1 |
| <i>Lasmiditan Free Base (LY573144)</i>                                 | 50                   | 100    |                   |                                      |
| Microcrystalline Cellulose <sup>a</sup><br>Cellulose, Microcrystalline | (b) (4)              |        | (b) (4)           | USP-NF, JP<br>Ph.Eur.                |
| Pregelatinized Starch<br>Starch, Pregelatinised                        |                      |        |                   | USP-NF, JPE<br>Ph.Eur.               |
| Croscarmellose Sodium                                                  |                      |        |                   | USP-NF, Ph.Eur., JP                  |
| Sodium Lauryl Sulfate<br>Sodium Laurilsulfate                          |                      |        |                   | USP-NF, JP<br>Ph.Eur.                |
| (b) (4)                                                                |                      |        |                   |                                      |
| Magnesium Stearate                                                     | (b) (4)              |        | (b) (4)           | USP-NF, Ph.Eur., JP                  |
| <b>Core Tablet Weight:</b>                                             | (b) (4)              |        |                   |                                      |
| <b>Film Coating</b>                                                    |                      |        |                   |                                      |
| (b) (4)                                                                |                      |        |                   | In house <sup>d</sup>                |
|                                                                        |                      |        |                   | In house <sup>d</sup>                |
|                                                                        |                      |        |                   | USP-NF, JP<br>Ph.Eur.                |
| <b>Total Tablet Weight:</b>                                            | 120.8                | 241.5  |                   |                                      |

(b) (4)

(b) (4)

## 2. BCS I CLASS DRUG:

### 2.1 High Solubility and High Permeability of Drug Substance:

Lasmiditan drug substance exhibits high solubility and high permeability. The Applicant reported that [REDACTED] (b) (4)

(b) (4) lasmiditan meet the solubility criteria for a BCS Class I drug substance, at a maximum clinical dose of 200 mg. [REDACTED] (b) (4)

(b) (4)

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**2.3 BCS Class-I Designation:**

The Applicant submitted a BCS Class-I designation request with supportive information and data to the IND 103420. The FDA granted the BCS Class I status to the proposed drug product, REYVOW™ Tablets (refer to the Advice Letter dated 8/2/2018 in DARRTS).

**3. PROPOSED DISINTEGRATION AND DISSOLUTION METHOD:****3.1 Disintegration Testing:**

The applicant proposed a disintegration testing (water as the disintegration medium, with disks) as a regulatory in-vitro method for the product release of REYVOW™ Tablets. The proposed acceptance criterion for the disintegration testing is NMT (b) (4).

The Applicant reported that water was selected as the disintegration medium for easy implementation and minimization of the use of acid. The similar disintegration time of uncoated tablets were observed in different media, with and without disks (Figure 4).

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(b) (4)



The Applicant provided tablet disintegration time results for the fresh REYVOW™ Tablets batches (Table 3). (b) (4)

**Table 3. Disintegration results for REYVOW™ Tablet batches representative of the commercial tablets**

| Batch Number   | Formulation | Stability Batch Number (If Applicable) | Dose Strength (mg) | Manufacturer   | Disintegration Result <sup>a</sup> |
|----------------|-------------|----------------------------------------|--------------------|----------------|------------------------------------|
| C905414        | T2          | --                                     | 50                 | PR01 Eli Lilly | (b) (4)                            |
| TSA00118       |             | --                                     | 50                 |                |                                    |
| C906022        |             | --                                     | 100                |                |                                    |
| TSA00218       |             | --                                     | 100                |                |                                    |
| TSA04117       |             | --                                     | 50                 |                |                                    |
| TSA04217       |             | --                                     | 100                |                |                                    |
| TSA04317       |             | --                                     | 100                |                |                                    |
| C815848 (YZWX) |             | C815848A                               | 50                 |                |                                    |
| C815849 (YZWZ) | C815849A    | 100                                    |                    |                |                                    |

Because the disintegration data for the stability time points were not provided in the original submission, therefore, in the Information Request dated 3/12/2019, the Applicant was asked to submit disintegration data for the stability samples. In the Response dated 3/26/2019, the Applicant provided disintegration data for the 50 mg and 100 mg commercial image tablets (T2) on primary stability samples of Batches C815848 and C815849 (Figure 7 and Table 4). The Applicant reported that disintegration testing was not included in the testing protocol for the primary stability studies conducted on the T1 tablets.

The proposed disintegration testing as a regulatory in-vitro method for the product release of REYVOW™ Tablets is acceptable. Based on the provided disintegration data, the proposed disintegration acceptance criterion of “NMT (b) (4)” for REYVOW™ Tablets, 50 mg and 100 mg is acceptable.

**3.2 Dissolution Testing:**

The proposed dissolution method for REYVOW™ Tablets, 50 mg and 100 mg, is as follows:

| <b>Proposed dissolution method for Lasmiditan Tablets, 50 mg and 100 mg</b> |                    |                    |                    |
|-----------------------------------------------------------------------------|--------------------|--------------------|--------------------|
| <b>USP Apparatus</b>                                                        | <b>Speed (rpm)</b> | <b>Medium/Temp</b> | <b>Volume (mL)</b> |
| USP 2 (paddle)                                                              | 75                 | 0.01N HCl/37 °C    | 500                |

It is noted that the Applicant did not propose conducting dissolution testing for quality control purpose [REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED] (b) (4). Dissolution acceptance criterion is not proposed.

**3.2.1 Selection of dissolution conditions:**

The proposed dissolution method for REYVOW™ Tablets is USP 2 at 75 rpm in 500 mL of 0.01N HCl medium.



(b) (4)

**Reviewer's Assessment:** Based on the above information, considering that REYVOW™ Tablets disintegrate within (b) (4) and more than (b) (4) % lasmiditan dissolves in solution within 15 minutes, this Reviewer considers that the Applicant's proposal to use

disintegration in lieu of dissolution to release REYVOW™ Tablets batches is reasonable and acceptable. This Reviewer considers this disintegration acceptance criterion of “NMT (b) (4)” is acceptable for this immediate release drug product.

**4. BRIDGING PRODUCTS THROUGHOUT DEVELOPMENT:**

**4.1 Different Product Formulations Used in Clinical Studies:**

The drug product used for the clinical program and registration stability studies is T1 tablet in three strengths of 50 mg, 100 mg, and 200 mg (Tables 5 and 6). The commercial drug product is designated as T2 tablet in two strengths of 50 mg and 100 mg. The T2 tablets and T1 tablets have the same (b) (4) composition and manufacturing process. The difference between the T2 tablets and T1 tablets are (b) (4)



**Table 5. Lasmiditan formulations used in clinical trials**

| Formulation                    | Manufacturing History | Clinical Use                                                   |                   |
|--------------------------------|-----------------------|----------------------------------------------------------------|-------------------|
| <b>T1 (Round White Tablet)</b> |                       | CoLucid Study Number                                           | Lilly Trial Alias |
| 50 mg                          | Oct 2008              | COL MIG-103                                                    | H8H-CD-LAHQ       |
|                                | Dec 2015              | COL MIG-105                                                    | H8H-CD-LAHP       |
|                                | Aug 2016              | COL MIG-106                                                    | H8H-CD-LAHG       |
|                                |                       | COL MIG-202                                                    | H8H-CD-LAHO       |
|                                |                       | COL MIG-302                                                    | H8H-CD-LAHK       |
| 100 mg                         | Oct 2014              | COL MIG-106                                                    | H8H-CD-LAHG       |
|                                | Apr 2015              | COL MIG-301                                                    | H8H-CD-LAHJ       |
|                                | Oct 2015              | COL MIG-302                                                    | H8H-CD-LAHK       |
|                                | Dec 2015              | COL MIG-305                                                    | H8H-CD-LAHL       |
|                                | Jul 2016              | N/A                                                            | H8H-MC-LAHB       |
|                                | May 2016              | N/A                                                            | H8H-MC-LAIF       |
|                                | Aug 2016<br>Nov 2016  | N/A                                                            | H8H-MC-LAIG       |
| 200 mg                         | Oct 2008              | COL MIG-103                                                    | H8H-CD-LAHQ       |
|                                | Oct 2014              | COL MIG-104                                                    | H8H-CD-LAHR       |
|                                | Apr 2015              | COL MIG-106                                                    | H8H-CD-LAHG       |
|                                | Oct 2015              | COL MIG-113                                                    | H8H-CD-LAHN       |
|                                | Dec 2015              | COL MIG-114                                                    | H8H-CD-LAHF       |
|                                | Jul 2016              | COL MIG-118                                                    | H8H-CD-LAHI       |
|                                | May 2016              | COL MIG-202                                                    | H8H-CD-LAHO       |
|                                | Aug 2016              | COL MIG-301                                                    | H8H-CD-LAHJ       |
|                                | Nov 2016              | COL MIG-302                                                    | H8H-CD-LAHK       |
|                                |                       | COL MIG-305                                                    | H8H-CD-LAHL       |
|                                |                       | N/A                                                            | H8H-MC-LAHA       |
|                                |                       | N/A                                                            | H8H-MC-LAHB       |
|                                |                       | N/A                                                            | H8H-MC-LAHC       |
|                                |                       | N/A                                                            | H8H-MC-LAHD       |
|                                |                       | N/A                                                            | H8H-MC-LAHE       |
| N/A                            |                       | H8H-MC-LAHT                                                    |                   |
| N/A                            |                       | H8H-MC-LAHU                                                    |                   |
| <b>T2 (Commercial Tablet)</b>  |                       | CoLucid Study Number                                           | Lilly Trial Alias |
| 50 mg                          | N/A                   | This formulation has not yet been used in any clinical studies |                   |
| 100 mg                         |                       |                                                                |                   |

**Table 6. Lasmiditan T1 tablet formulation (50-mg, 100-mg, and 200-mg strengths)**

| Ingredient                                          | Quantity (mg/tablet) |           |           | Function          |
|-----------------------------------------------------|----------------------|-----------|-----------|-------------------|
|                                                     | 50 mg                | 100 mg    | 200 mg    |                   |
| (b) (4)                                             |                      |           |           |                   |
| LY573144 (Lasmiditan Hemisuccinate <sup>a,b</sup> ) | 57.82 mg             | 115.64 mg | 231.28 mg | Active Ingredient |
| Microcrystalline Cellulose (b) (4)                  |                      |           |           | (b) (4)           |
| Starch (b) (4)                                      |                      |           |           |                   |
| Croscarmellose Sodium                               |                      |           |           |                   |
| Sodium Lauryl Sulfate                               |                      |           |           |                   |
| (b) (4)                                             |                      |           |           |                   |
| Magnesium Stearate                                  |                      |           |           | (b) (4)           |
| Total Core Tablet Weight                            |                      |           |           | --                |
| <b>Film Coating Components</b>                      |                      |           |           |                   |
|                                                     |                      |           |           |                   |
| Total Coated Tablet Weight                          | 115.3 mg             | 230.6 mg  | 461.3 mg  | --                |

**4.2 Comparative Dissolution Data for T2 and T1 formulations:**

In support of drug product comparability, the Applicant provided comparative dissolution data for T2 and T1 formulations (Figures 10–13).

**Reviewer's Assessment:** The provided comparative dissolution profile data support the product comparability of T2 and T1 formulations. This Reviewer considers that the bridging between two formulations is adequately established.

## **5. BRIDGING PRODUCTS MANUFACTURED AT DIFFERENT SITES:**

### **5.1 Different Product Manufacturing Sites:**

The initial manufacturing site for the proposed REYVOW™ Tablets primary stability batches is (b) (4). The Applicant added an alternative drug product manufacturing site of Eli Lilly del Caribe (Puerto Rico) for the commercial scale batches. The Applicant stated that the manufacturing process at both sites are the same.

### **5.2 Comparative Dissolution Data for REYVOW™ Tablets Formulations Manufactured at Different Sites:**

In support of drug product comparability, the Applicant provided comparative dissolution data for the formulations manufactured at different sites, using the dissolution method of USP Apparatus 2 at 75 rpm in 500 mL of 0.01N HCl medium (Tables 7 and 8).

**Table 7. Dissolution data for lasmiditan commercial tablets manufactured at the site of (b) (4)**

|                                    |                                     |                                   |                                   |
|------------------------------------|-------------------------------------|-----------------------------------|-----------------------------------|
| <b>Batch Number</b>                |                                     | <b>YZWX</b>                       | <b>YZWZ</b>                       |
| <b>Drug Substance Batch Number</b> |                                     | 2P2499C812                        | 2P2499C812                        |
| <b>Dosage (mg)</b>                 |                                     | 50                                | 100                               |
| <b>Batch Size (Tablets)</b>        |                                     | (b) (4)                           |                                   |
| <b>Manufacturing Site</b>          |                                     | (b) (4)                           |                                   |
| <b>Date of Manufacture</b>         |                                     | Sep 2017                          | Sep 2017                          |
| <b>Batch Use</b>                   |                                     | Primary Stability, Clinical Trial | Primary Stability, Clinical Trial |
| <b>Test</b>                        | <b>Proposed Acceptance Criteria</b> | <b>Results</b>                    |                                   |
| (b) (4)                            |                                     |                                   |                                   |

**Table 8. Dissolution data for lasmiditan commercial tablets manufactured at the site of Eli Lilly del Caribe (Puerto Rico)**

|                                    |                                     |                |                |               |             |             |             |
|------------------------------------|-------------------------------------|----------------|----------------|---------------|-------------|-------------|-------------|
| <b>Batch Number</b>                | C905414                             | TSA00118       | C906022        | TSA00218      | TSA04117    | TSA04217    | TSA04317    |
| <b>Drug Substance Batch Number</b> | C859935                             | C859935        | C859935        | C859935       | C815455     | C810651     | C810651     |
| <b>Dosage (mg)</b>                 | 50                                  | 50             | 100            | 100           | 50          | 100         | 100         |
| <b>Batch Size (Tablets)</b>        | (b) (4)                             |                |                |               | (b) (4)     |             |             |
| <b>Manufacturing Site</b>          | PR01                                | PR01           | PR01           | PR01          | PR01        | PR01        | PR01        |
| <b>Date of Manufacture</b>         | Mar 2018                            | Mar 2018       | Mar 2018       | Mar 2018      | Nov 2017    | Nov 2017    | Dec 2017    |
| <b>Batch Use</b>                   | Clinical Trial                      | Tech Transfer  | Clinical Trial | Tech Transfer | Development | Development | Development |
| <b>Test</b>                        | <b>Proposed Acceptance Criteria</b> | <b>Results</b> |                |               |             |             |             |
| (b) (4)                            |                                     |                |                |               |             |             |             |

**Reviewer’s Assessment:** The provided comparative dissolution data support the product comparability of REYVOW™ Tablets manufactured at the sites of (b) (4) and Eli Lilly del Caribe. This Reviewer considers the bridging among different manufacturing sites are adequately established.



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Zhao

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