NDA 211280

NDA APPROVAL

Eli Lilly and Company
Attention: Ana Vaz, MPH
Advisor, Global Regulatory Affairs
Lilly Corporate Center
Drop Code 2543
Indianapolis, Indiana 46285

Dear Ms. Vaz:

Please refer to your new drug application (NDA) dated and received October 11, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Reyvow (lasmiditan) 50 mg and 100 mg tablets.

This NDA provides for the use of Reyvow (lasmiditan) tablets for the acute treatment of migraine with or without aura in adults.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved for use as recommended in the enclosed agreed-upon labeling.

CONTROLLED SUBSTANCE SCHEDULING

You were previously informed that FDA intends to recommend scheduling of Reyvow under the Controlled Substances Act (CSA). The scheduling of this product in accordance with the CSA (21 U.S.C. 811) is not yet complete as of the date of this letter. Therefore, in accordance with the FDCA (21 U.S.C. 355(x)), the effective date of approval for Reyvow shall be the date on which the Drug Enforcement Administration (DEA) publishes a notice in the Federal Register announcing the interim final scheduling of lasmiditan.

We note that, when the drug is scheduled by the DEA, you will need to make appropriate revisions to the Prescribing Information, Medication Guide, and carton and container labeling by submitting a supplement to your NDA. This would include the statements in the labeling detailing the scheduling of lasmiditan as the scheduled substance in Reyvow, as required under 21 CFR 201.57(a)(2) and (c)(10)(i). Therefore, Reyvow may be marketed only after DEA has published the notice in the Federal Register announcing the interim final scheduling of lasmiditan and you submit a supplement to your NDA to revise all applicable drug labeling to reflect the drug scheduling described in the notice. For changes to the Prescribing Information, Medication Guide, and carton and container labeling to describe the scheduling of

lasmiditan, you can submit a Changes Being Effected supplement described in 21 CFR 314.70(c)(6). Permission to use a Changes Being Effected supplement for this purpose reflects a waiver by the Agency, pursuant to 21 CFR 314.90, of the requirement to submit a Prior Approval Supplement for changes to reflect the scheduling to the Highlights of Prescribing Information for Reyvow described in 21 CFR 314.70(b)(2)(v)(C) and changes to the Medication Guide described in 21 CFR 314.70(b)(2)(v)(B).

We note that Reyvow will be listed in the Orange Book upon the date of approval in accordance with 21 U.S.C. 355(x). With respect to the submission of patent information, as required under 21 CFR 314.53(c)(2)(ii), we note that you must submit Form FDA 3542 within 30 days after the date on which DEA has published the notice in the Federal Register announcing the interim final scheduling of lasmiditan.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on October 8, 2019, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 211280**." Approval of this submission by FDA is not required before the labeling is used.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

ADVISORY COMMITTEE

Your application for Reyvow was not referred to an FDA advisory committee because the clinical trial design was acceptable, the efficacy findings were clear, and the safety profile was acceptable for use in the intended population.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric studies requirement for children under 6 years of age because necessary studies are impossible or highly impracticable. This is because very few children of this age can be definitively diagnosed with migraine.

We are deferring submission of your pediatric studies for children and adolescents 6 to less than 18 years of age because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required under section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. These required studies are listed below.

3728-1 An open-label pharmacokinetics, safety, and tolerability study in pediatric migraine patients with body weight less than or equal to 40 kg. This study should identify doses to be used in the efficacy and long-term extension study for patients less than or equal to 40 kg.

Final Protocol Submission:	Submitted 04/2019
Study/Trial Completion:	07/2020
Final Report Submission:	10/2023

3728-2 A randomized, double-blind, placebo-controlled efficacy and safety study under PREA to evaluate two doses of Reyvow (high-dose and low-dose) compared to placebo in the acute treatment of migraine in pediatric patients ages 6 to less than 18 years. This study is to be submitted as a special protocol assessment (SPA).

Final Protocol Submission:	04/2020
Study/Trial Completion:	08/2022
Final Report Submission:	10/2023

3728-3 An open-label, long-term safety study under PREA in pediatric patients ages 6 to 18 years, for up to one year.

Final Protocol Submission:	04/2020
Study/Trial Completion:	09/2023
Final Report Submission:	10/2023

3728-4 Submission of the final study report for your completed juvenile animal toxicology study of lasmiditan in rat.

Final Report Submission	01/2020

Submit the protocols to your IND 103420, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify unexpected serious risks of adverse maternal, fetal, and infant outcomes resulting from the use of Reyvow during pregnancy.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

3728-5 Conduct prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with migraine exposed to Reyvow during pregnancy with two

unexposed control populations: one consisting of women with migraine who have not been exposed to Reyvow before or during pregnancy and the other consisting of women without migraine. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

The timetable you submitted on October 8, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	05/2020
Final Protocol Submission:	12/2020
Annual Interim Report Submissions:	12/2021
	12/2022
	12/2023
	12/2024
	12/2025
	12/2026
	12/2027
	12/2028
	12/2029
	12/2030
	12/2031
	12/2032
Study Completion:	12/2033
Final Report Submission:	12/2034

3728-6 Conduct a pregnancy outcomes study using a different study design than provided for in PMR 3728-5 (for example, a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in women exposed to Reyvow during pregnancy compared to an unexposed control population.

The timetable you submitted on October 8, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	05/2020
Final Protocol Submission:	12/2020
Annual Interim Report Submissions:	12/2021
	12/2022
	12/2023
	12/2024
	12/2025
	12/2026
Study Completion:	12/2027
Final Report Submission:	12/2028

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of drug interactions mediated by P-gp or BCRP.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

3728-7 Conduct a clinical drug interaction trial to evaluate the effect of Reyvow at its highest approved dose level on the pharmacokinetics of a sensitive P-gp substrate (e.g., digoxin) to address the potential for increased exposure and excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled, “Clinical Drug Interaction Studies —Study Design, Data Analysis, and Clinical Implications”.

The timetable you submitted on October 8, 2019, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	04/2020
Final Protocol Submission:	09/2020
Trial Completion:	06/2021
Final Report Submission:	12/2021

3728-8 Conduct a clinical drug interaction trial to evaluate the effect of Reyvow at its highest approved dose level on the pharmacokinetics of a sensitive BCRP substrate (e.g., rosuvastatin) to address the potential for increased exposure and excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Clinical Drug

Interaction Studies —Study Design, Data Analysis, and Clinical Implications".

The timetable you submitted on October 8, 2019, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	04/2020
Final Protocol Submission:	09/2020
Trial Completion:	06/2021
Final Report Submission:	12/2021

Submit clinical protocol(s) to your IND 103420 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312 or FDA's regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

REQUESTED PHARMACOVIGILANCE

We request that you perform postmarketing surveillance for myocardial infarction, stroke, malignancy, hypersensitivity, and serotonin syndrome after exposure to Reyvow. Include comprehensive summaries and analyses of these events quarterly as part of

your required postmarketing safety reports [e.g., periodic safety update reports (PSURs)]. Include analyses of the events by age and gender. In the analysis of each case, provide an assessment of causality, with documentation of risk factors and results of all assessments that support the diagnosis or the causality, along with extent of exposure to Reyvow and most recent exposure to Reyvow, concomitant therapies, treatment given for the event, and outcome. Include a comparison to background rates expected in a migraine population of the same age and gender.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the Prescribing Information, Medication Guide, and Patient Package Insert (as applicable) to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[6]

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

REPORTING REQUIREMENTS

You must comply with the reporting requirements described in 21 CFR 314.80(c)(1) (e.g., 15-day alert reports) beginning on the date of this letter. The due dates for the periodic (including quarterly) adverse drug experience reports described in 21 CFR 314.80(c)(2) should be calculated from the date of this letter. Annual reports described in 21 CFR 314.81(b)(2) are due within 60 days of the anniversary of the date of approval in accordance with 21 U.S.C. 355(x).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at FDA.gov.[7]

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, contact E. Andrew Papanastasiou, Regulatory Project Manager, by email at emilios.papanastasiou@fda.hhs.gov or by phone at (301) 796-1930.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Deputy Director (Acting)
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide

[7] http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm

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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/

WILLIAM H Dunn
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