NDA 022173/S-39

**SUPPLEMENT APPROVAL**

Eli Lilly and Company
Attention: Joseph D Orchowski, PharmD,
Consultant, Regulatory Scientist
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Orchowski:

Please refer to your supplemental new drug application (sNDA) dated and received March 8, 2021, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for for Zyprexa Relprevv (olanzapine pamoate) for Extended Release injectable suspension.

This Changes Being Effected supplemental new drug application provides for proposed modifications to the approved Zyprexa Relprevv (olanzapine pamoate) risk evaluation and mitigation strategy (REMS).

We have completed our review of this supplemental application, as amended. It is approved effective on the date of this letter.

## RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Zyprexa Relprevv (olanzapine pamoate) was originally approved on December 11, 2009, and the most recent REMS modification was approved on April 22, 2020. The REMS consists of a Medication Guide (MG), a communication plan (CP), elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modification to the REMS consists of updates to the Privacy Policy page of the Zyprexa Relprevv (olanzapine pamoate) Patient Care Program (PCP) Website to meet current requirements, including updating and hyperlinking of the California Privacy Policy Statement.

Your proposed modified REMS, submitted on March 8, 2021, appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on July 8, 2010.

The revised REMS assessment plan must include, but is not limited to, the following:

**Program Implementation and Operations**

1. REMS Program Operation and Performance Data (per reporting period beginning 31 August 2019 through 30 August 2020 and cumulatively)

    a. REMS Coordinating Call Center
        i. Number of contacts by stakeholder type (patients, healthcare providers, pharmacies, healthcare facilities, wholesaler/distributors, other)
        ii. Summary of reasons for calls (i.e. enrollment question, location of a certified healthcare facility) and by reporter (i.e. authorized representative, healthcare facility, patient/caregiver, other)
        iii. Summary of frequently asked questions (FAQ) by stakeholder type
        iv. Summary report of REMS-related problems identified and resulting corrective actions

2. REMS Enrollment Statistics (per reporting period beginning 31 August 2018 through 30 August 2019 and cumulatively, including retrospective data for the previous four reporting periods)

    a. Healthcare Providers
        i. Number of newly certified and active (have prescribed Zyprexa Relprevv for at least one patient during the reporting period) healthcare providers. Stratify by professional degree (MD, DO, NP, PA, Nurse, Other), medical specialty, and geographic regions.
        ii. Number of healthcare providers who retrained and recertified during the assessment period.

    b. Healthcare Facilities
        i. Number of newly certified and active (have administered at least one injection during the reporting period) healthcare facilities. Stratify by healthcare facility type (prescriber office, clinic/outpatient facility, hospital, other), and geographic region
        ii. Number of healthcare facilities who retrained and recertified during the assessment period.

    c. Pharmacy Service Providers
        i. Number of newly certified and active (have filled at least one prescription during the reporting period) pharmacies. Stratify by pharmacy type (community/retail, specialty, hospital/institution, or other), and geographic region.

ii. Number of dispensers who retrained and recertified during the assessment period.

d. Patients
   i. Number of newly enrolled and active patients (have received at least one injection during the reporting period). Stratify by age, gender, race and ethnicity.

3. Zyprexa Relprevv Utilization Data (per reporting period beginning 31 August 2018 through 30 August 2019 and cumulatively, including retrospective data for the previous four reporting periods)

   a. Number of vials distributed to certified dispensers stratified by pharmacy type (retail, specialty pharmacy, hospital, other) and to prescribers that purchase through buy and bill procedures.
   b. Number of prescriptions dispensed to certified healthcare settings. Stratify by:
      i. Pharmacy type (community/retail, specialty, hospital/institution, or other)
      ii. Prescriber specialty, provider degree/credentials, geographic region
      iii. Patient demographics (age, gender, race and ethnicity)
   c. Among the prescriptions dispensed, the number and proportion of prescriptions that came through buy and bill procedures.

4. REMS Compliance (per reporting period and cumulatively except as noted below)

   a. Provide a copy of the non-compliance plan used, including the criteria for non-compliance for each stakeholder, actions taken to address non-compliance for each case, and which event lead to de-certification from the REMS.
   b. Provide a copy of the audit plan for each stakeholder (Per reporting period beginning 31 August 2018 through 30 August 2019)
   c. A summary of non-compliance identified, including but not limited to (Per reporting period beginning 31 August 2019 through 30 August 2020):
      i. Report of audit findings for each stakeholder
         1. The number of audits expected, and the number of audits performed.
         2. The number and types of deficiencies noted for each group of audited stakeholders.
         3. For those with deficiencies noted, report the number that successfully completed a corrective and preventive action (CAPA) plan within one month of audit.
         4. For any that did not complete the CAPA within one month of the audit, describe actions taken.

5. Include a unique ID for each stakeholder that had deviations to track deviations by stakeholder over time.
6. Documentation of completion of training for relevant staff.
7. The existence of documented processes and procedures for complying with the REMS.

d. Healthcare facilities (For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken) (per reporting period beginning 31 August 2019 through 30 August 2020)
   i. Number and type of healthcare settings for which non-compliance with the REMS is detected
   ii. Number of times Zyprexa Relprevv was dispensed to an uncertified healthcare facility
   iii. Number and type of non-certified healthcare facility that administered Zyprexa Relprevv and the number of incidents for each healthcare facility
   iv. Number of healthcare facilities that did not have ready access to emergency responses that can allow for continuous patient monitoring for at least 3 hours post- injection
   v. Number of patients who were not enrolled prior to receiving Zyprexa Relprevv
   vi. Number of times Zyprexa Relprevv was administered without verifying that patient is enrolled
   vii. Number of healthcare settings de-certified for non- compliance and reasons for de-certification

e. Prescribers (per reporting period beginning 31 August 2019 through 30 August 2020)
   i. Number of prescriptions written and dispensed to a patient by a non-certified prescriber
   ii. Number of instances where prescribers have involuntarily discontinued prescribing Zyprexa Relprevv for patients who were unable to comply with the program requirements

f. Pharmacies (For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken) (per reporting period beginning 31 August 2019 through 30 August 2020)
   i. The number and type of pharmacies for which non-compliance with the REMS is detected
   ii. The number and type of non-certified pharmacies that dispensed Zyprexa Relprevv and the number of incidents for each
   iii. Number of times Zyprexa Relprevv was dispensed without appropriate verification (verifying that patient is enrolled and prescriber is certified)

iv. Number of pharmacies who were de-certified for non-compliance and reasons for de-certification.

g. Distributor
   i. The number of times Lilly distributed Zyprexa Relprevv to non-certified healthcare facility and non-certified dispenser.

5. Reports on Form
   a. Injection Forms
      i. Number of injection forms expected, received, and outstanding as of the report cut-off date
      ii. Number of injection forms not received within 7 days. Include outreach activities performed to collect the forms
      iii. Number of injections given by dosage strength

   b. Post Injection Delirium Sedation Syndrome (PDSS Form) (per reporting period beginning 31 August 2018 through 30 August 2019 and cumulatively, including retrospective data for the previous four reporting periods)
      i. Number of PDSS forms expected, received, and outstanding as of the report cut-off date
      ii. Number of PDSS forms not received within 24 hours. Include outreach activities performed to collect the forms

**Safe Use Behaviors** (per reporting period beginning 31 August 2018 through 30 August 2019 and cumulatively, including retrospective data for the previous four reporting periods)

1. Number of patients who were not observed for at least 3 hours after injection. Include the number of healthcare facility, proportion of events per patient and per injection, and cumulative number of events and patients and proportion of events per patient and per injection.

2. Number of patients who left the healthcare facility unaccompanied after injection. Include the number of healthcare facility, proportion of events per patient and per injection, and cumulative number of events and patients and proportion of events per patient and per injection.

**Knowledge**

1. Evaluation of healthcare providers and patients (or caregivers) understanding of the risks of PDSS and the need for continuous observation of patients for at least three hours in certified healthcare facilities.

**Health Outcomes**

1. Safety Surveillance (per reporting period beginning 31 August 2018 through 30 August 2019 and cumulatively, including retrospective data for the previous four reporting periods)

    a) Known, or suspected adverse events related PDSS are to be reported regardless of outcome. Root cause analyses of whether REMS processes for patient monitoring were followed are to be included. Sources of the reports are to include but not be limited to:
        i. Injection Forms
            1. Number of PDSS cases occurring in patients
            2. Number of patients experiencing PDSS
            3. Number of active patients and injections in the REMS
            4. PDSS cases/dose level administered (210 mg, 300 mg, 405 mg, other dosage amount)
            5. Proportion of PDSS events per patient
            6. Proportion of PDSS events per injection
            7. Cumulative numbers of patients, injections, and PDSS events
            8. Cumulative proportion of PDSS events per patient and PDSS events per injection
            9. Number of adverse everts and PDSS events linked to patients who were not observed for three hours
            10. Number of adverse events and PDSS events linked to patients who left the healthcare facilities (HCF) unaccompanied
            11. Trend analysis of whether adverse events decrease or increase over time
        ii. PDSS Forms
        iii. Adverse events reported in the REMS Registry
        iv. Spontaneous adverse event reports
            12. Include the search strategy used to identify cases (via safety database) and specific Medical Dictionary for Regulatory Activities (MedDRA) terms used to identify cases of interest
            13. Include a line listing of all cases that includes: manufacturer control number, narrative, assessment of causality, and source of the report
        v. Literature searches
        vi. Social media
        vii. Include an overall summary and discussion of whether the data warrants further detailed assessment, labeling changes, and/or communication.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent

to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the

submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 022173 REMS ASSESSMENT METHODOLOGY**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

**NDA 022173 REMS ASSESSMENT**

***or***

**NEW SUPPLEMENT FOR NDA 022173/S-000**
**CHANGES BEING EFFECTED IN 30 DAYS**
**PROPOSED MINOR REMS MODIFICATION**

***or***

**NEW SUPPLEMENT FOR NDA 022173/S-000**
**PRIOR APPROVAL SUPPLEMENT**
**PROPOSED MAJOR REMS MODIFICATION**

***or***

**NEW SUPPLEMENT FOR NDA 022173S-000/**
**PRIOR APPROVAL SUPPLEMENT**
**PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX**

***or***

**NEW SUPPLEMENT (NEW INDICATION FOR USE)**
**FOR NDA 022173/S-000**
**REMS ASSESSMENT**
**PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

**REMS REVISIONS FOR NDA 022173**

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

**SUBMISSION OF REMS DOCUMENT IN SPL FORMAT**

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

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**REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Ermias Zerislassie, Regulatory Project Manager, at 301-797-2770.

Sincerely,

*{See appended electronic signature page}*

Marc Stone, M.D.
Deputy Director for Safety
Division of Psychiatry
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- REMS

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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.**

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/s/

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