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NDA 22-173
Zyprexa® Relprevv™ (olanzapine)

For Extended Release Injectable Suspension

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RISK EVALUATION AND MITIGATION STRATEGY (REMS)

Zyprexa Relprevv Patient Care Program

I. GOAL

The goal of the Zyprexa Relprevv Patient Care Program is to mitigate the risk of negative outcomes associated with Zyprexa Relprevv post-injection delirium/sedation syndrome (PDSS) by:

1. ensuring Zyprexa Relprevv is prescribed only by certified prescribers, dispensed only by certified dispensers, and dispensed for use only in certified healthcare facilities with ready access to emergency response services, and dispensed for use only with documentation of safe use conditions;
2. informing healthcare providers and patients about the risks and the need for continuous observation of patients for at least 3 hours in certified health care facilities; and
3. establishing long-term safety and safe use of Zyprexa Relprevv through periodic monitoring for the risk of PDSS events and by enrolling all patients who receive Zyprexa Relprevv in the Zyprexa Relprevv Patient Care Program Registry.

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide is dispensed with each Zyprexa Relprevv prescription in accordance with 21 CFR 208.24.

The Medication Guide is part of the REMS and is appended.

B. Communication Plan

In accordance with the United States (US) Federal Food, Drug, and Cosmetic Act (FDCA) 505-1(e)(3), Lilly issued a Dear Healthcare Professional Letter which targeted psychiatrists as well as pharmacies within 60 days of product approval to support the implementation of the Zyprexa Relprevv Patient Care Program and the conditions of safe use. The Dear Healthcare Professional Letter was issued by mass mailing one time at product launch.

C. Elements to Assure Safe Use

Lilly commits to implement the following elements to assure safe use that includes requirements applicable to prescribers, pharmacies, and other third parties as described below:

1. **Healthcare providers who prescribe Zyprexa Relprevv are specially certified under 505-1(f)(3)(A).**

   a. Lilly will ensure that prescribers enrolled in the Zyprexa Relprevv Patient Care Program are specially certified. Lilly will ensure that, to become certified, prescribers attest to their understanding of the Zyprexa Relprevv Patient Care Program requirements and the risks associated with Zyprexa Relprevv, have completed the mandatory Zyprexa Relprevv training, and have attested that they:

      i. understand the clinical presentation of post-injection delirium/sedation syndrome (PDSS) and how to manage patients should an event occur while using Zyprexa Relprevv;

      ii. understand that Zyprexa Relprevv should only be initiated in patients for whom tolerability with oral olanzapine has been established;

      iii. understand that Zyprexa Relprevv should only be administered to patients in health care settings (e.g. , hospitals, clinics) that have ready access to emergency response services and that can allow for continuous patient monitoring for at least 3 hours post-injection;

      iv. will enroll all patients in the Zyprexa Relprevv Patient Care Program Registry prior to prescribing Zyprexa Relprevv by completing the Patient Registration Form;

      v. will review the Zyprexa Relprevv Medication Guide with each patient or the patient's legal guardian prior to prescribing; and,

      vi. understand that the Zyprexa Relprevv Patient Care Program coordinating center may contact the prescriber to resolve discrepancies, to obtain information about a patient, or to conduct occasional surveys.

   b. The certified prescriber will be retrained and recertified every 3 years from time of enrollment.

   c. Lilly may disenroll prescribers that are noncompliant with the program requirements.

d. Lilly will maintain a validated and secured database of all certified prescribers, as well as a database of the completed data forms. The database links each reported PDSS event to the enrolled patient and the associated prescriber.

e. The following prescriber materials are part of the REMS and are appended:

1. Healthcare Professional Training
2. Zyprexa Relprevv Patient Care Program Instructions Brochure
3. Prescriber Registration Form

2. Zyprexa Relprevv will only be dispensed by pharmacies and health-care settings under FDCA 505-1(f)(3)(C) who are specially certified under FDCA 505-1(f)(3)(B).

a. Lilly will ensure that to be certified to dispense Zyprexa Relprevv, each pharmacy and health-care setting will be enrolled in the Zyprexa Relprevv Patient Care Program. Lilly will ensure that to become enrolled the pharmacy and health-care setting staff have been educated about the requirements of the Zyprexa Relprevv Patient Care Program.

The education and enrollment process is comprised of the following steps that must be completed:

i. Each pharmacy and health-care setting where Zyprexa Relprevv is dispensed for use in other certain health-care settings will designate a representative who will review the Zyprexa Relprevv Patient Care Program Instruction Brochure. The designated representative will complete and sign the Pharmacy Registration Form or the Buy and Bill Registration Form. In signing the form, the representative is required to indicate that they understand and attest that:

a) I have read and understand the Zyprexa Relprevv Patient Care Program Instructions Brochure;

b) I will ensure that all appropriate pharmacy staff are trained and have read and understand the Zyprexa Relprevv Patient Care Program Instructions Brochure;

c) I will ensure that all appropriate pharmacy staff understand that Zyprexa Relprevv can only be dispensed for use in certain health care settings (e.g., hospitals, clinics) that have ready access to emergency response services that can allow for continuous patient monitoring for at least 3 hours post-injection;

d) I will ensure that pharmacy staff will verify that the patient is enrolled in the Zyprexa Relprevv Patient Care Program Registry prior to dispensing each prescription/refill by accessing the system;

e) I will ensure that pharmacy staff will not dispense Zyprexa Relprevv directly to patients;

f) I will ensure pharmacy staff report the date of each Zyprexa Relprevv dispensing to the Zyprexa Relprevv Patient Care Program; and

g) I understand that the Zyprexa Relprevv Patient Care Program coordinating center may contact the pharmacy to clarify information provided or obtain information about the patient.

ii. Each health-care setting where Zyprexa Relprevv is dispensed and administered to the patient will designate a representative who will review the Zyprexa Relprevv Patient Care Program Instruction Brochure. The designated representative will complete and sign the Healthcare Facility Registration Form. In signing the form, the representative is required to indicate that they understand and attest that:

a) I have read and understand the Zyprexa Relprevv Patient Care Program Instructions Brochure;

b) I will ensure that all appropriate staff are trained and have read and understand the Zyprexa Relprevv Patient Care Program Instructions Brochure;

c) I will ensure that all appropriate staff understand that Zyprexa Relprevv can only be dispensed for use in certain health-care settings (e.g., hospitals, clinics) that have ready access to emergency response services that can allow for continuous patient monitoring for at least 3 hours post-injection;

d) I will ensure the health-care setting has systems, protocols, or other measures to ensure that Zyprexa Relprevv is only administered to patients enrolled in the program and that patients are continuously monitored for at least 3 hours post-injection for suspected PDSS;

e) I will ensure that appropriate staff will verify that the patient is enrolled in the Zyprexa Relprevv Patient Care Program Registry prior to each injection by accessing the system;

f) I will ensure that the Medication Guide is provided to the patient or the patient's legal guardian prior to each injection;

g) I will ensure that the appropriate staff monitors the patient continuously for at least 3 hours; and

h) I understand that the Zyprexa Relprevv Patient Care Program coordinating center may contact the health-care setting to clarify information provided or obtain information about the patient.

b. Certified dispensers will be recertified every 3 years from the time of enrollment.

c. Lilly may disenroll dispensers that are noncompliant with the program requirements.

d. The following materials are part of the REMS and are appended:

1. Pharmacy Registration Form
2. Buy & Bill Pharmacy Service Provider Registration Form
3. Zyprexa Relprevv Healthcare Professional Training
4. Zyprexa Relprevv Reconstitution and Administration Training
5. Zyprexa Relprevv Patient Care Program Instructions Brochure
6. Healthcare Facility Registration Form

3. Zyprexa Relprevv will be dispensed to patients with evidence or other documentation of safe-use conditions under FDCA 505-1(f)(3)(D).

a. Lilly will ensure that certified dispensers will verify that each patient is eligible to receive Zyprexa Relprevv prior to dispensing each prescription/refill of Zyprexa Relprevv by accessing the Zyprexa Relprevv Patient Care Program and ensuring the patient is enrolled in the Zyprexa Relprevv Patient Care Program Registry and the prescriber is certified.

4. Each patient using Zyprexa Relprevv will be subject to certain monitoring under 505-1(f)(3)(E).

a. For each injection of Zyprexa Relprevv, the practitioner or health-care facility staff that administers Zyprexa Relprevv must monitor the patient continuously for at least 3 hours.

5. Each patient using the drug will be enrolled in a registry under 505-1(f)(3)(F).

a. Lilly will ensure that certified prescribers enroll each patient treated with Zyprexa Relprevv in the Zyprexa Relprevv Patient Care Program Registry and assign a unique identifying number before Zyprexa Relprevv is dispensed to each enrolled patient. Unless otherwise excepted under section 5e, Lilly will ensure that, to become enrolled, each patient or patient's legal guardian signs the Patient Registration Form indicating that:

i. they understand that the patient must enroll in the Zyprexa Relprevv Patient Care Program Registry to receive Zyprexa Relprevv;

ii. they agree to have patient information entered in the Zyprexa Relprevv Patient Care Program Registry;

iii. the doctor has explained the risk and benefits of treatment with Zyprexa Relprevv;

iv. they have received a copy of the Medication Guide;

v. they understand that the patient will be observed at the clinic for 3 hours after each injection;

vi. they understand that the patient must be accompanied from the health-care facility to their destination;

vii. they understand that the patient must not use heavy machinery for the rest of the day on which the injection was administered;

viii. they agree to seek medical care right away if the patient has a reaction such as excessive sleepiness, dizziness, confusion, difficulty talking, difficulty walking, muscle stiffness or shaking, weakness, irritability, aggression, anxiety, increase in blood pressure or convulsions;

ix. they agree to contact the physician if the patient has a reaction to Zyprexa Relprevv; and

x. they may be asked to complete occasional surveys about their understanding of the risks and benefits of treatment with Zyprexa Relprevv.

b. Lilly will ensure that health-care settings where Zyprexa Relprevv is administered record and submit the following information for each patient after each injection by completing either the Single or Multiple Patient Injection Form and returning this form to the Zyprexa Relprevv Patient Care Program coordinating center:

i. injection date and time;

ii. dose;

iii. verification that the patient was continuously observed at the healthcare facility for at least 3 hours;

iv. verification that the patient was alert, oriented, and absent of any signs and symptoms of PDSS prior to being released from the health-care facility;

v. verification that the patient was accompanied upon leaving the health-care facility;

vi. verification that the patient or the patient's legal guardian was given a Medication Guide prior to this injection;

vii. any report of a PDSS event since the previous Zyprexa Relprevv injection; and

viii. verification that the health-care setting contacted the prescriber if the patient experienced a PDSS event.

c. Lilly will ensure that certified prescribers record and submit the following information for any report of PDSS in a patient administered Zyprexa Relprevv by completing the Post-Injection Delirium/Sedation Form and returning it to the Zyprexa Relprevv Patient Care Program coordinating center:

   i. summary of the PDSS event, including signs and symptoms of any event and a detailed timeline of the course of events related to injection;

   ii. demographic characteristics of the patient (age, gender, race, height, weight, medical conditions, geographical location);

   iii. Zyprexa Relprevv dose;

   iv. type and timing of interventional treatment or therapy administered;

   v. outcome of the PDSS event;

   vi. concomitant medications prior to and at the time of PDSS occurrence; and

   vii. preexisting or concurrent medical conditions.

d. The following materials are part of the REMS and are appended:

   1. Patient Registration Form

   2. Single Patient Injection Form

   3. Multiple Patient Injection Form

   4. Post-Injection Delirium/Sedation Syndrome Form

e. In situations where a patient is under a court order for involuntary psychiatric treatment, which order permits the administration of medications without patient consent and/or against the patient's wishes, and where no guardian has been appointed for the patient, such patient may be enrolled in the Zyprexa Relprevv Patient Care Program Registry without patient signature. However, the Patient Registration Form must clearly show that said court order is in place and the duration of the court order. The information required under section 5(a) iii should still be shared with the patient, and the provisions of sections 5b,5c, and 5d shall still apply.

f. Patients enrolled under section 5e shall be considered enrolled only until such time that their court order for involuntary treatment terminates, or they are discharged from their involuntary commitment by their treatment team where permitted by applicable state law. Upon such termination or discharge, the patient must be re-enrolled in the Zyprexa Relprevv Patient Care Program pursuant to the requirements of section 5a to be eligible for continued treatment with Zyprexa Relprevv. In the alternative, if an involuntary commitment is extended by court order, a new Patient Registration Form should be requested reflecting the duration of the new order.

D. Implementation System

The Implementation System will include the following. Lilly will:

1) Maintain a validated and secured database of all certified dispensers, as well as a database of the completed data forms. The database links each reported PDSS event to the enrolled patient and the associated dispenser.
2) Review distribution data to assess compliance with the requirement that Zyprexa Relprevv is only dispensed by the certified dispensers.
3) Assess certified dispensers' compliance with the requirement to dispense Zyprexa Relprevv for use in health-care settings that have ready access to emergency response services and can allow for continuous patient monitoring for at least 3 hours post-injection.
4) Based on evaluation of the implementation of elements to assure safe use provided for under Sections C2 and C3 above, and in the manner described in the REMS supporting document, take reasonable steps to improve implementation of these elements to meet the goals of the REMS.

E. Timetable for Submission of Assessments

Lilly will submit REMS assessments to the FDA annually on 29 October. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Lilly will submit each assessment so that it will be received by the FDA on or before the due date.