NDA 22-173 Zyprexa® Relprevv™ (olanzapine)

For Extended Release Injectable Suspension

Eli Lilly and Company

Indianapolis, IN 46285

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

Zyprexa Relprevv Patient Care Program

I. GOALS

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 health care providers and patients about the risks and the need for continuous observation of patients for at least 3 hours in certified healthcare 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 prescription for Zyprexa Relprevv in accordance with 21 CFR 208.24 and by the Healthcare Provider (HCP) as described below.

Lilly will include the Medication Guide inside each Zyprexa Relprevv convenience kit which is a single unit of dispensing. The Medication Guide will also be available on the Zyprexa Relprevv Patient Care Program website.

Please see appended Medication Guide.

B. Communication Plan

In accordance with the United States (US) Federal Food, Drug, and Cosmetic Act (FDCA) 505-1(e)(3), Lilly will issue a Dear Healthcare Professional Letter to 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 will be issued by mass mailing one time at product launch.

The Dear Healthcare Professional Letter is part of the REMS and is appended.

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 healthcare 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 prior to prescribing;

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 non-compliant 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 healthcare 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 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 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;

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 prior to each injection;

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

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 non-compliant 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 healthcare facility staff that administers Zyprexa Relprevv must monitor the patient continuously for at least 3 hours.

5. Each patient using the drug 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. Lilly will ensure that, to become enrolled, each patient or patient's 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 healthcare 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;

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 healthcare 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 healthcare facility;

v. verification that the patient was accompanied upon leaving the healthcare facility;

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

vii. verification that the healthcare 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;

vii. pre-existing 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

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 FDA according to the schedule below. 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.

REMS Assessment Data Cutoff Date	**REMS Assessment Due Date And Receipt Date**
31 March 2010	30 May 2010
30 August 2010	29 October 2010
30 August 2011	29 October 2011
Annually on 30 August	Annually on 29 October

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22173	SUPPL-4	ELI LILLY CO	ZYPREXA/ADHERA

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/s/

THOMAS P LAUGHREN
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