

Initial REMS Approval: 12/2009
Most Recent Modification: 10/2014

NDA 22-173
Zyprexa[®] Relprevv[™] (olanzapine)

For Extended Release Injectable Suspension

Eli Lilly and Company
Lilly Corporate Center, Indianapolis, Indiana 46285
Telephone: 317-276-2000

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.

PHARMACY REGISTRATION FORM



To be enrolled in the ZYPREXA RELPREVV Patient Care Program, complete and fax this form to 1-877-772-9391.

Training must be completed before a pharmacy may be enrolled in the ZYPREXA RELPREVV Patient Care Program.

PHARMACY INFORMATION

Enrollment Reenrollment

Pharmacy/Hospital Name: _____

Pharmacy DEA Number: _____

Please specify description of Pharmacy: Community/Retail Specialty Pharmacy Hospital or Institution Other

Address Line 1: _____

Address Line 2: _____

City: _____ State: _____ Zip: _____

Primary Phone: _____ Secondary Phone: _____

Fax: _____

SHIP TO INFORMATION

Ship To Address (if the same as above, check here)

Ship To Contact Name: _____

Address Line 1: _____

Address Line 2: _____

City: _____ State: _____ Zip: _____

Primary Phone: _____ Secondary Phone: _____

Fax: _____

PHARMACIST-IN-CHARGE INFORMATION

First Name: _____ MI: _____ Last Name: _____

Email: _____

Phone: _____ Fax: _____
(if different from above) (if different from above)

PHARMACIST-IN-CHARGE INFORMATION

By signing below, I acknowledge that:

- I have read and understand the ZYPREXA RELPREVV Patient Care Program Instructions Brochure.
- I will ensure that all appropriate pharmacy staff are trained and have read and understand the ZYPREXA RELPREVV Patient Care Program Instructions Brochure.
- 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 and that can allow for continuous patient monitoring for at least 3 hours post-injection.
- 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.
- I will ensure that pharmacy staff will not dispense ZYPREXA RELPREVV directly to patients.
- I will ensure pharmacy staff report the date of each ZYPREXA RELPREVV dispensing to the ZYPREXA RELPREVV Patient Care Program.
- For each dispense I will ensure prescription verification (includes patient eligibility check and recording the dispense date) is completed on the date of dispense, prior to the convenience kit leaving the pharmacy.
- 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.

I may cancel this registration by notifying the ZYPREXA RELPREVV Patient Care Program Coordinating Center by fax at 1-877-772-9391 or by phone at 1-877-772-9390. If I cancel, Lilly will cease to supply ZYPREXA RELPREVV to the pharmacy.

Pharmacist-in-Charge Signature Date:

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month day year

PHONE 1-877-772-9390

FAX 1-877-772-9391

www.zyprexarelprevvprogram.com

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BUY & BILL* PHARMACY SERVICE PROVIDER REGISTRATION FORM

BUY & BILL
PHARMACY



To be enrolled in the ZYPREXA RELPREVV Patient Care Program, complete and fax this form to 1-877-772-9391.

Training must be completed before a pharmacy service provider may be enrolled in the ZYPREXA RELPREVV Patient Care Program.

PHARMACY SERVICE PROVIDER INFORMATION

Enrollment Reenrollment

Facility Name: _____

DEA Number: _____

Please specify description of Pharmacy: Community/Retail Specialty Pharmacy Hospital or Institution Other

Address Line 1: _____

Address Line 2: _____

City: _____ State: _____ Zip: _____

Primary Phone: _____ Secondary Phone: _____

Fax: _____

SHIP TO INFORMATION

Ship To Address (if the same as above, check here)

Ship To Contact Name: _____

Address Line 1: _____

Address Line 2: _____

City: _____ State: _____ Zip: _____

Primary Phone: _____ Secondary Phone: _____

Fax: _____

ADMINISTRATOR INFORMATION

First Name: _____ MI: _____ Last Name: _____

Preferred Method of Communication: Email Fax

Email: _____

Phone: _____ Fax: _____
(if different from above) (if different from above)

PHARMACY SERVICE PROVIDER AGREEMENT

By signing below, I acknowledge that:

- I have read and understand the ZYPREXA RELPREVV Patient Care Program Instructions Brochure.
- I will ensure that all appropriate pharmacy staff are trained and have read and understand the ZYPREXA RELPREVV Patient Care Program Instructions Brochure.
- 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 and that can allow for continuous patient monitoring for at least 3 hours post-injection.
- 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.
- I will ensure that pharmacy staff will not dispense ZYPREXA RELPREVV directly to patients.
- I will ensure pharmacy staff report the date of each ZYPREXA RELPREVV dispensing to the ZYPREXA RELPREVV Patient Care Program.
- For each dispense I will ensure prescription verification (includes patient eligibility check and recording the dispense date) is completed on the date of dispense, prior to the convenience kit leaving the pharmacy.
- I understand that the ZYPREXA RELPREVV Patient Care Program Coordinating Center may contact the pharmacy to clarify information provided or to obtain information about the patient.

I may cancel this registration by notifying the ZYPREXA RELPREVV Patient Care Program Coordinating Center by fax at 1-877-772-9391 or by phone at 1-877-772-9390. If I cancel, Lilly will cease to supply ZYPREXA RELPREVV to the facility.

Administrator Signature Date:

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month day year

*Buy & Bill Pharmacy Service Provider - a licensed healthcare provider that purchases pharmaceuticals through a licensed distributor for its own use in the treatment of a patient and then includes the cost of the pharmaceutical in its billing of patients and third-party payers.

PHONE 1-877-772-9390

FAX 1-877-772-9391

www.zyprexarelprevvprogram.com

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PRESCRIBER REGISTRATION FORM



To be enrolled in the ZYPREXA RELPREVV Patient Care Program, complete and fax this form to 1-877-772-9391.

Training must be completed before a prescriber may be enrolled in the ZYPREXA RELPREVV Patient Care Program.

PRESCRIBER INFORMATION

Enrollment Reenrollment

First Name: _____ MI: _____ Last Name: _____

Degree: MD DO NP PA Nurse with prescriptive authority Other with prescriptive authority

License Number: _____ State of Issue: _____

Treatment Facility/Practice (Where you see your patients): _____

If you see your patients at multiple locations please contact the ZYPREXA RELPREVV Patient Care Program Coordinating Center to provide additional facility/practice information

Address Line 1: _____

Address Line 2: _____

City: _____ State: _____ Zip: _____

Phone: _____ Alternate Phone: _____

Fax: _____ Prescriber Email: _____

Preferred Method of Communication: Email Fax

PRESCRIBER AGREEMENT

By signing below, I acknowledge that:

- I understand the ZYPREXA RELPREVV Patient Care Program requirements and the risks associated with ZYPREXA RELPREVV.
- I have completed the mandatory ZYPREXA RELPREVV training.
- 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;
- I understand that ZYPREXA RELPREVV should only be initiated in patients for whom tolerability with oral olanzapine has been established;
- I 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.
- I will enroll all patients in the ZYPREXA RELPREVV Patient Care Program registry prior to prescribing ZYPREXA RELPREVV by completing the Patient Registration Form.
- I will ensure all suspected cases of PDSS are reported to the ZYPREXA RELPREVV Patient Care Program within 24 hours of becoming aware of the event.
- I will review the ZYPREXA RELPREVV Medication Guide with each patient prior to prescribing.
- I understand that the ZYPREXA RELPREVV Patient Care Program Coordinating Center may contact me to resolve discrepancies, to obtain information about a patient, or to conduct occasional surveys.

I may cancel this registration by notifying the ZYPREXA RELPREVV Patient Care Program Coordinating Center by fax at 1-877-772-9391 or by phone at 1-877-772-9390.

If I revoke my registration, I will no longer be eligible to prescribe ZYPREXA RELPREVV.

Lilly may disenroll prescribers that are non-compliant with the program requirements.

Prescriber Signature

Date:

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month day year



HEALTHCARE FACILITY REGISTRATION FORM



To be enrolled in the ZYPREXA RELPREVV Patient Care Program, complete and fax this form to 1-877-772-9391.

Training must be completed before a healthcare facility may be enrolled in the ZYPREXA RELPREVV Patient Care Program.

HEALTHCARE FACILITY INFORMATION

Enrollment Reenrollment

Healthcare Facility Name: _____

Please specify location of Healthcare Facilities: Prescriber Office Clinic/Outpatient Facility Hospital Other

Address: _____

City: _____ State: _____ Zip: _____

Phone: _____ Fax: _____

AUTHORIZED HEALTHCARE FACILITY REPRESENTATIVE INFORMATION

First Name: _____ MI: _____ Last Name: _____

Position/Title: _____

Phone: _____ Fax: _____

Email: _____

Preferred Method of Communication: Email Fax

You may identify Delegate(s) to enter the necessary patient data into the Patient Care Program system.

Delegate First Name: _____ MI: _____ Last Name: _____

Facility Name: _____

Phone: _____ Fax: _____
(if different from above) (if different from above)

Email: _____

Delegate First Name: _____ MI: _____ Last Name: _____

Facility Name: _____

Phone: _____ Fax: _____
(if different from above) (if different from above)

Email: _____

Delegate First Name: _____ MI: _____ Last Name: _____

Facility Name: _____

Phone: _____ Fax: _____
(if different from above) (if different from above)

Email: _____

Delegate First Name: _____ MI: _____ Last Name: _____

Facility Name: _____

Phone: _____ Fax: _____
(if different from above) (if different from above)

Email: _____

Delegate First Name: _____ MI: _____ Last Name: _____

Facility Name: _____

Phone: _____ Fax: _____
(if different from above) (if different from above)

Email: _____

If additional Delegates are required contact the the Patient Care Program Coordinating Center.

PHONE 1-877-772-9390

FAX 1-877-772-9391

www.zyprexarelprevvprogram.com



HEALTHCARE FACILITY REGISTRATION FORM

HEALTHCARE FACILITY AGREEMENT

As the authorized representative for this facility, I attest that:

- I have read and understand the ZYPREXA RELPREVV Patient Care Program Instructions Brochure;
- I will ensure that all appropriate staff are trained and have read and understand the ZYPREXA RELPREVV Patient Care Program Instructions Brochure as well as the following Training Materials:
 - ZYPREXA RELPREVV Healthcare Professional Training
 - ZYPREXA RELPREVV Reconstitution and Administration Training
- 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 and that can allow for continuous patient monitoring for at least 3 hours post-injection;
- 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;
- 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;
- I will ensure that the Medication Guide is provided to the patient or the patient's legal guardian prior to each injection;
- I will ensure that the appropriate staff monitors the patient continuously for at least 3 hours;
- I will ensure that required data are submitted within 7 days after each injection to the ZYPREXA RELPREVV Patient Care Program.
- I understand that the ZYPREXA RELPREVV Patient Care Program Coordinating Center may contact the health care setting to clarify information provided or to obtain information about the patient.

I confirm that the information above is correct.

I understand that this information will be used to document healthcare facilities that are eligible to administer ZYPREXA RELPREVV.

I also understand that this information may be shared with government agencies.

I understand that Lilly will regularly evaluate ZYPREXA RELPREVV Patient Care Program compliance to ensure that program objectives are met. Lilly reserves the right to terminate a healthcare facility's enrollment at any time based upon non-compliance or to take other appropriate measures to assure that the ZYPREXA RELPREVV Patient Care Program objectives are met.

I may cancel this healthcare facility registration in the future by notifying Lilly in writing and submitting the notification by fax to 1-877-772-9391 or by calling 1-877-772-9390. If I revoke this facility's registration, the facility will no longer be eligible to administer ZYPREXA RELPREVV to patients.

Authorized Healthcare Facility Representative Signature

Date:

<input type="text"/>	<input type="text"/>	-	<input type="text"/>	<input type="text"/>	-	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
month			day			year			

Authorized Healthcare Facility Representative Name (print) _____ Title _____

Please fax completed form to the ZYPREXA RELPREVV Patient Care Program at 1-877-772-9391.

PHONE 1-877-772-9390

FAX 1-877-772-9391

www.zyprexarelprevvprogram.com

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Reference ID: 3673779

PATIENT REGISTRATION FORM



To be enrolled in the ZYPREXA RELPREVV Patient Care Program, complete and fax this form to 1-877-772-9391.

PATIENT INFORMATION

First Name: _____ MI: _____ Last Name: _____

Date of Birth: _____

Gender: Male Female

Race: White Black or African American Native Hawaiian or Other Pacific Islander
 Asian American Indian or Alaska Native Other

Ethnicity: Hispanic or Latino
 Non-Hispanic/Non-Latino

PRESCRIBER INFORMATION

First Name: _____ MI: _____ Last Name: _____

License Number: _____ State of Issue: _____

Treatment Facility/Practice Name (where you see the patient): _____

Address Line 1: _____

Address Line 2: _____

Will the patient be injected/monitored at your facility/practice?

- Yes
 No (If No, complete next section)

INJECTING/MONITORING FACILITY INFORMATION

Facility Name (where the patient receives injections or monitoring): _____

Address Line 1: _____

Address Line 2: _____

City: _____ State: _____ Zip: _____

PATIENT AGREEMENT

The maker of ZYPREXA RELPREVV, Eli Lilly and Company and their delegates run the ZYPREXA RELPREVV Patient Care Program.

Your doctor will send your name, date of birth, and other information that directly identifies you to the ZYPREXA RELPREVV Patient Care Program. Ask your doctor if you have questions about the information that will be collected.

The ZYPREXA RELPREVV Patient Care Program will collect and use your information in the following ways:

- Your doctor will provide dose, date and time of each injection, and other medical information to the ZYPREXA RELPREVV Patient Care Program.
- Your information will be stored in the ZYPREXA RELPREVV Patient Care Program computer system.
- The information will be used to help Lilly learn more about the safety of ZYPREXA RELPREVV.
- Information from all patients in the ZYPREXA RELPREVV Patient Care Program will be reviewed and may be combined with information from clinical studies.
- This combined information will not be able to identify you or any other patient. This combined information may be shared with:
 - regulatory agencies,
 - doctors at other institutions,
 - the committee overseeing the ZYPREXA RELPREVV Patient Care Program, and/or
 - publications or as part of scientific discussions.

Also, by signing this form you agree to the following:

- I understand that I must enroll in the ZYPREXA RELPREVV Patient Care Program registry to get ZYPREXA RELPREVV.
- I agree to have my information entered in the ZYPREXA RELPREVV Patient Care Program registry.
- My doctor has explained the risks and benefits of treatment with ZYPREXA RELPREVV.
- I have received a copy of the Medication Guide.
- I understand that I will be observed at the clinic for 3 hours after each injection.
- Someone must go with me to my destination when I leave the clinic.
- I understand that I can not drive or use heavy machinery for the rest of the day on which I get an injection.
- I agree to seek medical care right away if I have 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.
- I agree to contact my doctor if I have a reaction to ZYPREXA RELPREVV.
- I may be asked to complete occasional surveys about my understanding of the risks and benefits of treatment with ZYPREXA RELPREVV.
- I or my caregiver have discussed any questions or concerns about my treatment with ZYPREXA RELPREVV with my doctor.

You may stop participating in the ZYPREXA RELPREVV Patient Care Program at any time by telling your doctor. If you stop participating, you will no longer be able to receive the drug. Your doctor will no longer provide any of your information to the ZYPREXA RELPREVV Patient Care Program except to answer safety questions. The ZYPREXA RELPREVV Patient Care Program will still use information that was collected before you stopped participating. You will be provided a copy of this form.

Signature

Date:

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 -

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 -

--	--	--	--

month day year

Printed Name of Patient

Printed Name of Legal Guardian (if applicable)

Check the box if the patient has not signed due to enrollment decision being made by prescriber who is authorized via a court order.
Date of Court Order Expiration (MMDDYYYY) _____

This patient has been shown to be tolerant of oral olanzapine.

Signature of Prescriber

Date:

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 -

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 -

--	--	--	--

month day year

Printed Name of Prescriber



SINGLE PATIENT INJECTION FORM



IMPORTANT: Before administering the injection, confirm there will be someone to accompany the patient after the 3-hour observation period. If this cannot be confirmed, do not give the injection.

Submit this information within 7 days after the patient's injections. If you are aware that the patient's prescriber has changed, please notify the ZYPREXA RELPREVV Patient Care Program Coordinating Center.

Patient No.: (PIN)

Injection Facility Name:

Patient Name: _____
 First _____ MI _____ Last _____

Date of Birth: - -
 month day year

PDSS since the last visit? (After the patient left the office, following his/her previous injection, did the patient experience post-injection delirium/sedation syndrome?)

No Yes

If Yes, has the prescriber been notified of the PDSS event?

Yes No

ZYPREXA RELPREVV TREATMENT

Date of Injection: - -
 month day year

Time of ZYPREXA RELPREVV injection: :
 24-hour clock

Dose of Injection: 150 mg 210 mg 300 mg 405 mg Other dose _____ mg

Was the patient observed for at least 3 hours post-injection? Yes No

Did the patient experience post-injection delirium/sedation syndrome during the onsite post-injection observational period?

No Yes

If Yes, has the prescriber been notified of the PDSS event? Yes No

Following the injection, was the patient alert, oriented, and absent of any signs and symptoms of PDSS prior to being released from the healthcare facility?

Yes No

Following the injection, was the patient accompanied from the facility?

Yes No Not applicable, patient did not leave facility (in-patient)

Was the patient or legal guardian given a Medication Guide prior to this injection? Yes No

Healthcare Facility Staff Member Signature _____ DATE: - -
 month day year

Healthcare Facility Staff Member Name (print): _____



MULTIPLE PATIENT INJECTION FORM

INJECTION
Multiple Patients



IMPORTANT: Before administering the injection, confirm there will be someone to accompany the patient after the 3-hour observation period. If this cannot be confirmed, do not give the injection.

Submit this information within 7 days after the patient's injection. If you are aware that the patient's prescriber has changed, please notify the ZYPREXA RELPREVV Patient Care Program Coordinating Center.

Injection Facility Name: _____

Date of Injection month day year
 - -

	Patient Info.	Patient Info.	Patient Info.
Patient No.: (PIN)	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
Patient Name:	First Name _____ MI _____ Last Name _____	First Name _____ MI _____ Last Name _____	First Name _____ MI _____ Last Name _____
Date of Birth:	mon h - day - year ____ - ____ - ____	month - day - year ____ - ____ - ____	month - day - year ____ - ____ - ____
PDSS since last visit? (check one)	<input type="checkbox"/> Yes <input type="checkbox"/> No If Yes, has the prescriber been notified of the PDSS event? <input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No If Yes, has the prescriber been notified of the PDSS event? <input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No If Yes, has the prescriber been notified of the PDSS event? <input type="checkbox"/> Yes <input type="checkbox"/> No
Time of Injection (24-hour clock)	<input type="text"/> : <input type="text"/>	<input type="text"/> : <input type="text"/>	<input type="text"/> : <input type="text"/>
Dose of Injection (check one)	<input type="checkbox"/> 150 mg <input type="checkbox"/> 210 mg <input type="checkbox"/> 300 mg <input type="checkbox"/> 405 mg <input type="checkbox"/> Other dose _____ mg	<input type="checkbox"/> 150 mg <input type="checkbox"/> 210 mg <input type="checkbox"/> 300 mg <input type="checkbox"/> 405 mg <input type="checkbox"/> Other dose _____ mg	<input type="checkbox"/> 150 mg <input type="checkbox"/> 210 mg <input type="checkbox"/> 300 mg <input type="checkbox"/> 405 mg <input type="checkbox"/> Other dose _____ mg
Observed at least 3 hours post-injection? (check one)	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
PDSS during onsite observation? (check one)	<input type="checkbox"/> Yes <input type="checkbox"/> No If Yes, has the prescriber been notified of the PDSS event? <input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No If Yes, has the prescriber been notified of the PDSS event? <input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No If Yes, has the prescriber been notified of the PDSS event? <input type="checkbox"/> Yes <input type="checkbox"/> No
Following the injection, was the patient alert, oriented, and absent of any signs and symptoms of PDSS prior to being released from the healthcare facility? (check one)	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
Following the injection, was the patient accompanied from the facility? (check one)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable, patient did not leave facility (in-patient)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable, patient did not leave facility (in-patient)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable, patient did not leave facility (in-patient)
Signature	_____ Healthcare Facility Staff Member Signature <input type="text"/> - <input type="text"/> - <input type="text"/> month day year _____ Healthcare Facility Staff Member Name (print)	_____ Healthcare Facility Staff Member Signature <input type="text"/> - <input type="text"/> - <input type="text"/> month day year _____ Healthcare Facility Staff Member Name (print)	_____ Healthcare Facility Staff Member Signature <input type="text"/> - <input type="text"/> - <input type="text"/> month day year _____ Healthcare Facility Staff Member Name (print)
Was the patient or legal guardian given a Medication Guide prior to this injection?	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No

Phone 1-877-772-9390

FAX 1-877-772-9391

www.zyprexareprevvprogram.com

Version 2.0 August 2012

CONFIDENTIAL

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Reference ID: 3675779



POST-INJECTION DELIRIUM/SEDATION SYNDROME (PDSS) FORM



Submit this information within **24 hours** of becoming aware of a suspected PDSS event.

Patient No.: (PIN)

Patient Name: _____
First Name MI Last Name

Date of Birth: - -
month day year

Does the patient have a diagnosis of schizophrenia? Yes No

PATIENT/INJECTION INFORMATION

Date of Injection: - -
month day year

Convenience Kit Package

Lot # _____

Time of ZYPREXA RELPREVV Injection: :
24-hour clock

ONSET OF FIRST PDSS SYMPTOM AFTER INJECTION (choose only one)

- | | | |
|--|--|---|
| <input type="checkbox"/> 1 - 15 minutes | <input type="checkbox"/> 46 - 60 minutes | <input type="checkbox"/> 121 - 150 minutes (2 ½ hours) |
| <input type="checkbox"/> 16 - 30 minutes | <input type="checkbox"/> 61 - 90 minutes (1 ½ hours) | <input type="checkbox"/> 151 - 180 minutes (3 hours) |
| <input type="checkbox"/> 31 - 45 minutes | <input type="checkbox"/> 91 - 120 minutes (2 hours) | <input type="checkbox"/> If greater than 3 hours please specify:
_____ Hours |

Dose of Injection: 150 mg 210 mg 300 mg 405 mg Other dose _____ mg

Was the injection given in gluteal muscle? Yes No

Height: (inches) Weight: (lbs.)

PDSS SIGNS AND SYMPTOMS

Please mark the signs and symptoms that the patient experienced (check all that apply).

- | | | | |
|---|---|--|--|
| <input type="checkbox"/> Aggressiveness | <input type="checkbox"/> Coma | <input type="checkbox"/> Hypertension | <input type="checkbox"/> Tachycardia |
| <input type="checkbox"/> Agitation | <input type="checkbox"/> Confusion | <input type="checkbox"/> Hypotension | <input type="checkbox"/> Various extrapyramidal symptoms |
| <input type="checkbox"/> Anxiety | <input type="checkbox"/> Convulsion/Seizure | <input type="checkbox"/> Other cognitive impairment | <input type="checkbox"/> Weakness |
| <input type="checkbox"/> Aspiration | <input type="checkbox"/> Delirium | <input type="checkbox"/> Possible neuroleptic malignant syndrome | <input type="checkbox"/> Other _____ |
| <input type="checkbox"/> Ataxia | <input type="checkbox"/> Disorientation | <input type="checkbox"/> Reduced level of consciousness | <input type="checkbox"/> Other _____ |
| <input type="checkbox"/> Cardiac arrhythmias | <input type="checkbox"/> Dizziness | <input type="checkbox"/> Respiratory depression | <input type="checkbox"/> Other _____ |
| <input type="checkbox"/> Cardiopulmonary arrest | <input type="checkbox"/> Dysarthria | <input type="checkbox"/> Sedation | <input type="checkbox"/> Other _____ |

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POST-INJECTION DELIRIUM/SEDATION SYNDROME (PDSS) FORM

Patient No.: (PIN)

Patient Name: _____
First Name MI Last Name

PDSS start date: - -
month day year

PDSS resolution date: - - OR Ongoing
month day year

If resolved, duration of PDSS: _____ Minutes Hours Days

Are these PDSS symptoms related to ZYPREXA RELPREVV?

Yes

No - Please Explain _____

Describe the clinical course _____

Patient Outcome: (choose one) Recovered Fatal Not Recovered
 Unknown Recovering Recovered with sequelae

Once a PDSS event was suspected, was the patient's monitoring initiated in a facility capable of resuscitation? Yes No

Did the patient visit the emergency room as a result of the PDSS? Yes No

Was the patient admitted to the hospital as a result of the PDSS? Yes No

Were olanzapine concentrations collected? Yes No

Did the patient receive any **MEDICATIONS AS TREATMENT** for the PDSS event? Yes - Please record below No

Treatment Medication Name	Dose	Duration of Use (in Days)

POST-INJECTION DELIRIUM/SEDATION SYNDROME (PDSS) FORM

Patient No.:

(PIN)

Patient Name: _____
 First Name MI Last Name

Did the patient receive any **NON-PHARMACEUTICAL TREATMENTS** or **DIAGNOSTIC TESTS** associated with this event? Yes - Please record below No

- | | | | |
|---|------------------------------------|---|--|
| <input type="checkbox"/> Assisted ventilation | <input type="checkbox"/> EEG | <input type="checkbox"/> MRI | <input type="checkbox"/> Urine drug screen |
| <input type="checkbox"/> Brain CT | <input type="checkbox"/> IV fluids | <input type="checkbox"/> Observation/symptomatic management | <input type="checkbox"/> Vital sign monitoring |
| <input type="checkbox"/> ECG | <input type="checkbox"/> Labs | <input type="checkbox"/> Restraints | <input type="checkbox"/> Other _____ |

Please fax test results to 1-877-772-9391.

HISTORY PRIOR TO PDSS EVENT

Does the patient have any relevant comorbidities?

- Yes - Please specify: _____
- No

PRIOR MEDICATIONS

Did the patient take any medications during the 24 hours prior to the injection? Yes - Please record below No

Prior Medication Name	Dose	Duration of Use			
		Number	Choose One		
			<input type="checkbox"/> Days	<input type="checkbox"/> Months	<input type="checkbox"/> Years
			<input type="checkbox"/> Days	<input type="checkbox"/> Months	<input type="checkbox"/> Years
			<input type="checkbox"/> Days	<input type="checkbox"/> Months	<input type="checkbox"/> Years
			<input type="checkbox"/> Days	<input type="checkbox"/> Months	<input type="checkbox"/> Years
			<input type="checkbox"/> Days	<input type="checkbox"/> Months	<input type="checkbox"/> Years

Did the patient use any of the following during the 24 hours prior to the injection? Yes - Please record below No

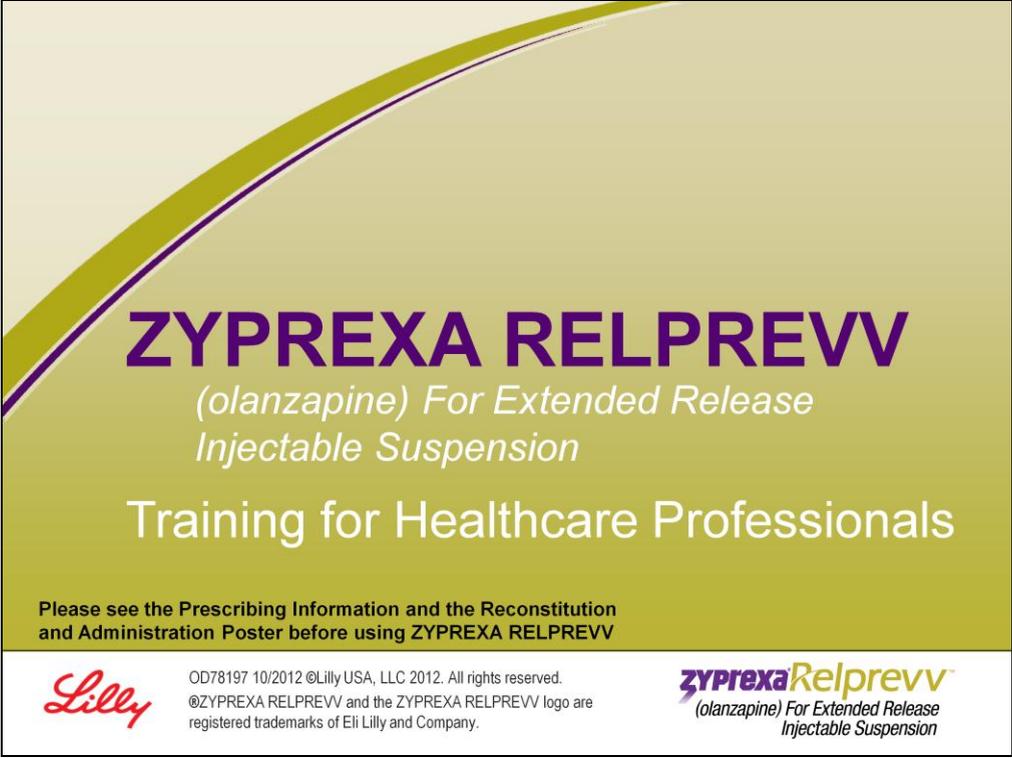
- | | | | |
|--|---------------------------------------|--|--|
| <input type="checkbox"/> Alcohol | <input type="checkbox"/> Barbiturates | <input type="checkbox"/> Cocaine | <input type="checkbox"/> Opiates |
| <input type="checkbox"/> Amphetamines/Methamphetamines | <input type="checkbox"/> Cannabinoid | <input type="checkbox"/> Hallucinogens | <input type="checkbox"/> Phencyclidine |

Event reported by: _____
 First MI Last

Title/Occupation: _____

If agent of the Prescriber, name of Prescriber: _____





ZYPREXA RELPREVV
*(olanzapine) For Extended Release
Injectable Suspension*

Training for Healthcare Professionals

Please see the Prescribing Information and the Reconstitution and Administration Poster before using ZYPREXA RELPREVV

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**ZYPREXA Relprevv**
*(olanzapine) For Extended Release
Injectable Suspension*

The goal of this presentation is to educate healthcare professionals in an effort to mitigate negative outcomes associated with ZYPREXA RELPREVV post-injection delirium/sedation syndrome (PDSS). Healthcare professionals include: physicians, nurses and any other professionals who will be involved with the care of the patient receiving the injection.

Please see the Prescribing Information and the Reconstitution and Administration Poster before using ZYPREXA RELPREVV.

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ZYPREXA RELPREVV: Indication

- ZYPREXA RELPREVV is a long-acting atypical antipsychotic for intramuscular injection indicated for the treatment of schizophrenia

For a list of symptoms and the complete diagnostic criteria for schizophrenia, see the *Diagnostic and Statistical Manual of Mental Disorders, Ed 4, Text Revision* (American Psychiatric Association; 2000).

For complete safety profile, including boxed warnings, see the full Prescribing Information.

Version 2.0 03-Aug-2012

zyprexaRelprevv
(olanzapine) For Extended Release
Injectable Suspension

ZYPREXA® RELPREVV™, also known as (olanzapine) For Extended Release Injectable Suspension, is the long-acting injectable form of ZYPREXA (olanzapine).

ZYPREXA RELPREVV is indicated for the treatment of schizophrenia and is administered by deep intramuscular gluteal injection.

ZYPREXA RELPREVV: Boxed Warnings

- **Post-injection Delirium/Sedation Syndrome (PDSS):**
 - Patients are at risk for severe sedation (including coma) and/or delirium after each injection and must be observed for at least 3 hours in a registered facility with ready access to emergency response services. Because of this risk, ZYPREXA RELPREVV is available only through a restricted distribution program called ZYPREXA RELPREVV Patient Care Program and requires prescriber, healthcare facility, patient, and pharmacy enrollment
- **Increased mortality in elderly patients with dementia-related psychosis:**
 - Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death
 - ZYPREXA RELPREVV is not approved for the treatment of patients with dementia-related psychosis

For complete safety profile, including boxed warnings, see the full Prescribing Information.

Version 2.0 03-Aug-2012

ZYPREXA Relprevv
(olanzapine) For Extended Release
Injectable Suspension

If you prescribe ZYPREXA RELPREVV, you need to be aware that it carries a boxed warning for Post-Injection Delirium/Sedation Syndrome (PDSS). Patients who receive ZYPREXA RELPREVV are at risk for severe sedation (including coma) and/or delirium after each injection and must be observed for at least 3 hours in a registered facility with ready access to emergency response services. Because of this risk, ZYPREXA RELPREVV is available only through a restricted distribution program called ZYPREXA RELPREVV Patient Care Program and requires prescriber, healthcare facility, patient, and pharmacy enrollment.

Because the active ingredient of ZYPREXA RELPREVV is the same as oral ZYPREXA® (olanzapine), ZYPREXA RELPREVV also carries the same boxed warning as oral ZYPREXA regarding increased mortality in elderly patients with dementia-related psychosis. ZYPREXA RELPREVV is not approved for the treatment of patients with dementia-related psychosis.

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Training Content

At the end of this training, you should be able to:

- ✓ Differentiate between ZYPREXA RELPREVV (olanzapine for extended release injectable suspension) and ZYPREXA IntraMuscular (olanzapine for injection) to avoid medication errors
- ✓ Understand the dosing options with ZYPREXA RELPREVV
- ✓ Know the common adverse events associated with ZYPREXA RELPREVV and how to monitor patients for metabolic changes
- ✓ Identify a post-injection delirium/sedation syndrome (PDSS) event in your clinical practice
- ✓ Know the conditions of safe use and how to manage the risk of PDSS
- ✓ Know what to do in case a PDSS event occurs
- ✓ Understand basics of the ZYPREXA RELPREVV Patient Care Program

For complete safety profile, including boxed warnings, see the full Prescribing Information. **ZYPREXA Relprevv**
(olanzapine) For Extended Release
Injectable Suspension

Version 2.0 03-Aug-2012

At the end of this training, you should be able to:

- Differentiate between ZYPREXA RELPREVV (olanzapine for extended release injectable suspension) and ZYPREXA IntraMuscular (olanzapine for injection) to avoid medication errors,
- Understand the dosing options with ZYPREXA RELPREVV.
- Know the common adverse events associated with ZYPREXA RELPREVV and how to monitor for metabolic changes
- Identify a post-injection delirium/sedation syndrome event in your clinical practice,
- Know the conditions of safe use and how to manage the risk of post-injection delirium/sedation syndrome
- Know what to do in case a post-injection delirium/sedation syndrome event occurs.
- And finally, understand the basics of the ZYPREXA RELPREVV Patient Care Program.

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ZYPREXA RELPREVV and ZYPREXA IntraMuscular –
Although both have olanzapine as their active ingredient and both are injected intramuscularly, they are intended for different indications and different dosing schedules

Category	ZYPREXA RELPREVV	ZYPREXA IntraMuscular
Indication	Treatment of schizophrenia	Agitation associated with schizophrenia and bipolar mania in adults
Generic Name	(olanzapine) For Extended Release Injectable Suspension	olanzapine for injection
Formulation	olanzapine pamoate suspension	olanzapine solution
Injection technique	IM, gluteal only	IM
Doses	150 mg/2wk, 210 mg/2wk, 405 mg/ 4wk, 300 mg/2wk	2.5 mg, 5 mg, 7.5 mg, 10 mg
Vial cap color & package lettering	terra cotta (210 mg), olive (300 mg), or blue (405 mg)	purple
Reconstitution	with special diluent provided in kit	with sterile water for injection
Appearance of medication in syringe	opaque yellow	clear yellow

For complete safety profile, including boxed warnings, see the full Prescribing Information.

Version 2.0 03-Aug-2012




It should be noted that there are 2 types of injectable olanzapine, and they are intended for very different purposes. ZYPREXA RELPREVV is the **long**-acting salt formulation of olanzapine, olanzapine pamoate, and is administered every 2 to 4 weeks for the treatment of schizophrenia in adults. ZYPREXA IntraMuscular is the **rapid**-acting injectable form of olanzapine and is indicated for the immediate treatment of **AGITATION** associated with schizophrenia or bipolar mania.

It is very important not to confuse these two products, so please also make note of the visual differences in the products and product packaging as well as differences in injection technique and dosing.

ZYPREXA RELPREVV: Formulation

- **Olanzapine pamoate salt**
 - Olanzapine plus pamoic acid
 - Crystalline
 - Insoluble in water
- **Why use pamoate salts?**
 - Decreases solubility
 - Extended delivery
 - Long action up to 4 weeks
 - No known pharmacological activity
 - Excreted unchanged
 - Used in other approved products



For complete safety profile, including boxed warnings, see the full Prescribing Information.

Version 2.0 03-Aug-2012

ZYPREXA Relprevv
(olanzapine) For Extended Release
Injectable Suspension

ZYPREXA RELPREVV is a combination of olanzapine and pamoic acid in the form of a crystalline salt, which is insoluble in water but has very low solubility in muscle. When injected into the gluteal muscle, the salt then dissolves slowly at the site of the injection. This results in a slow and sustained release of olanzapine into the bloodstream, allowing for administration once every 2 or 4 weeks.

The pamoic acid component allows for this extended delivery but has no known pharmacological activity and is excreted unchanged. It has been used in a number of other approved products.

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ZYPREXA RELPREVV: Product Characteristics

- **Deep intramuscular gluteal injection only**
 - 19 gauge 1.5" needle (2" needle may be used for obese patients)
 - Not for deltoid injection
- **3 vial strengths – 210 mg, 300 mg, 405 mg**
 - Describes the available olanzapine in that vial
 - Reconstitute with the diluent provided to a fixed concentration of 150 mg/mL
 - 24-hour medication stability in vial once reconstituted
 - No refrigeration needed
- **Inject immediately after withdrawing from vial**



Review the ZYPREXA RELPREVV Reconstitution and Administration Training Video and the Reconstitution and Administration Poster before reconstituting the product

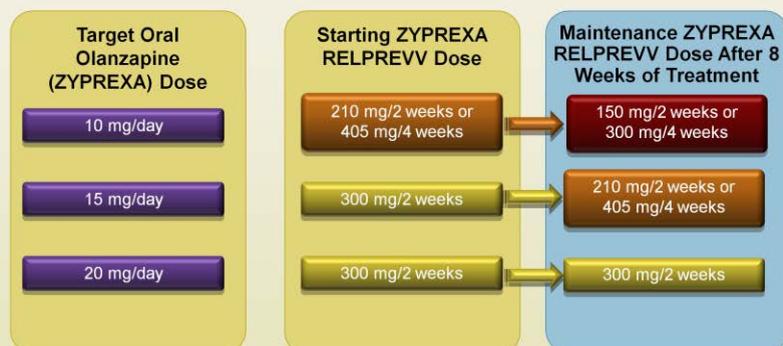
For complete safety profile, including boxed warnings, see the full Prescribing Information. **ZYPREXA Relprevv**
(olanzapine) For Extended Release
Injectable Suspension

Version 2.0 03-Aug-2012

- ZYPREXA RELPREVV is administered by deep intramuscular gluteal injection only, using a 19 gauge, 1.5" needle to ensure a deep gluteal injection and to prevent the suspension from clogging the needle. A 2" needle may be used for obese patients. Please note that ZYPREXA RELPREVV is not approved for deltoid injections.
- ZYPREXA RELPREVV is provided as olanzapine pamoate powder, which comes in 3 vial strengths: 210, 300, and 405 mg. These strengths describe the amount of olanzapine provided in each vial. The product must be reconstituted using the diluent provided, which contains a wetting agent, a thickening agent, and an isotonic agent to allow for easier reconstitution and administration as well as patient comfort. Both the powder and the diluent are stored at room temperature and are reconstituted to a fixed concentration of 150 mg of olanzapine per milliliter.
- Once reconstituted, the suspension is stable in the vial for up to 24 hours and does not require refrigeration. However, if the suspension is not used immediately, it should be shaken to resuspend before being withdrawn into the syringe for administration.
- Once the product has been withdrawn from the vial, it should be injected immediately.
- Review the ZYPREXA RELPREVV Reconstitution and Administration Training Video and the Reconstitution and Administration Poster before reconstituting the product

Dosing of ZYPREXA RELPREVV

Recommended Dosing for ZYPREXA RELPREVV Based on Correspondence to Oral Olanzapine (ZYPREXA) Doses



For complete safety profile, including boxed warnings, see the full Prescribing Information.

Version 2.0 03-Aug-2012

zyprexa
Olanzapine

zyprexaRelprevv
(olanzapine) For Extended Release
Injectable Suspension

Transition

- How does ZYPREXA RELPREVV correspond to an oral olanzapine dose?
- This figure depicts the approximate dose correspondence between oral olanzapine and ZYPREXA RELPREVV

Key points

- Dosing of ZYPREXA RELPREVV is described by the number of milligrams of active ingredient—olanzapine—provided in each injection; for instance, a 150 mg ZYPREXA RELPREVV dose contains 150 mg of olanzapine
- After the first 8 weeks of treatment when plasma concentrations approach steady state levels, there is a clear dose correspondence with oral olanzapine
 - This correspondence can be estimated by dividing the number of milligrams by the number of days in the dosing interval; thus:
 - 150 mg of ZYPREXA RELPREVV given every 2 weeks or 300 mg given every 4 weeks corresponds to approximately 10 mg/day of oral olanzapine
 - 210 mg of ZYPREXA RELPREVV given every 2 weeks or 405 mg given every 4 weeks corresponds to approximately 15 mg/day of oral olanzapine
 - 300 mg of ZYPREXA RELPREVV given every 2 weeks corresponds to approximately 20 mg/day of oral olanzapine
- During the first 8 weeks of treatment, a loading dose strategy is recommended for the 10 or 15 mg/day patients
- Please refer to the Package Insert for complete dosing information

9

Comparable Safety Profile Between ZYPREXA RELPREVV and Oral Olanzapine: 24-Week Study

Treatment-Emergent Adverse Events: Incidence >2% with ZYPREXA RELPREVV

	ZYPREXA RELPREVV (N=599) %	Oral Olanzapine (N=322) %
Patients with ≥1 TEAE	52.1	46.9
Weight Increased	7.2	7.5
Insomnia	7.2	4.0
Nasopharyngitis	4.3	4.3
Anxiety	4.8	2.8
Headache	3.2	4.3
Somnolence	3.8	2.8
Injection site pain	2.3	0.9
Hallucination	2.3	0.6

None of these events were statistically significantly different

Adverse events reported with ZYPREXA RELPREVV were consistent with adverse events reported with oral olanzapine, taking into account method of administration. Data on file, Lilly Research Laboratories, ZYP20081111D

For complete safety profile, including boxed warnings, see the full Prescribing Information.

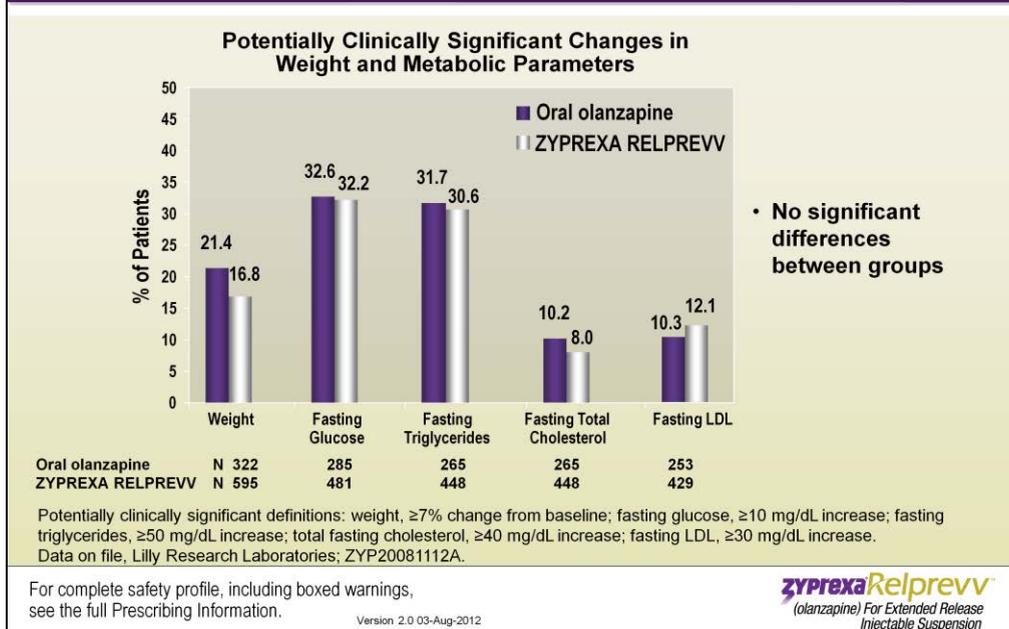


(olanzapine) For Extended Release
Injectable Suspension

Version 2.0 03-Aug-2012

Now we will look at the safety profile for ZYPREXA RELPREVV. The overall safety of ZYPREXA RELPREVV is similar to that of oral olanzapine, with the exception of injection-related events. In a study of over 900 stabilized patients comparing ZYPREXA RELPREVV and oral olanzapine, there were no significant differences in the most commonly reported adverse events. Weight gain was the most commonly reported event in both groups.

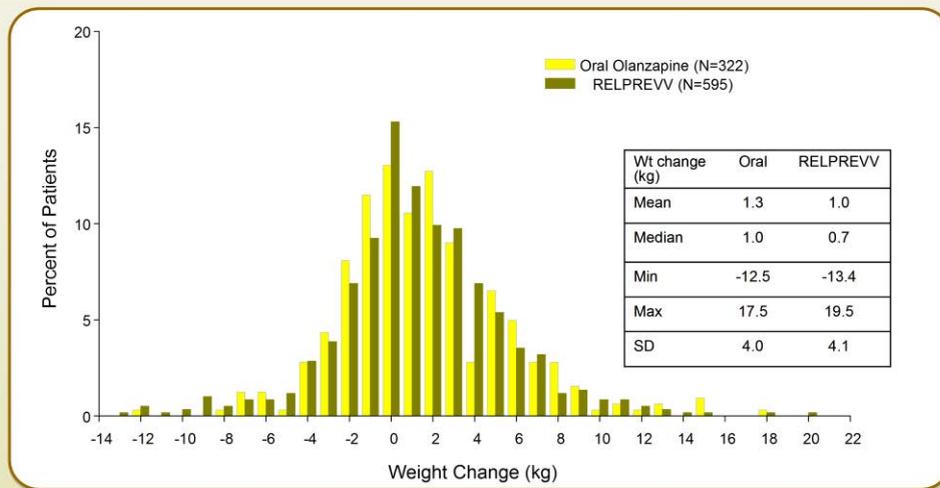
Metabolic Changes Similar to Oral Olanzapine in the 24-Week Study



Data from the 24-week study comparing ZYPREXA RELPREVV to oral olanzapine also indicated no significant differences in the percentage of patients experiencing a potentially clinically significant change from baseline in weight, fasting glucose, fasting triglycerides, fasting total cholesterol, or fasting LDL cholesterol.

The results suggest that the metabolic profile is comparable to that of oral olanzapine.

Similar Weight Change Between ZYPREXA RELPREVV and Oral Olanzapine Over 24 Weeks



Note that baseline is after 4-8 wks on oral olanzapine. Mean weight gain during this lead in period was 1.06 kg.

Oral = Oral olanzapine.

Data on file, Lilly Research Laboratories, ZYP20081112D

For complete safety profile, including boxed warnings, see the full Prescribing Information.

Version 2.0 03-Aug-2012

ZYPREXA Relprevv
 (olanzapine) For Extended Release
 Injectable Suspension

Looking at the weight change seen in this study in more detail, there was no difference in the pattern of weight gain or loss in patients treated with ZYPREXA RELPREVV versus those treated with oral olanzapine. The mean weight change in both groups was a gain of approximately one kilogram.

Differences by Dose with ZYPREXA RELPREVV

In a 24-week randomized, double-blind, fixed-dose study comparing 3 doses of ZYPREXA RELPREVV in patients with schizophrenia, statistically significant differences among dose groups were observed for the safety parameters below.

	Increasing ZYPREXA RELPREVV Dose →		
	150 mg/2 wk	405 mg/4 wk	300 mg/2 wk
Weight (kg) ^a	0.67	0.89	1.70*
Prolactin (µg/L) ^a	-5.61	-2.76	3.57*†
Fasting triglycerides ^b	6.5%	9.8%	24.5%*†

^a Mean change

^b Change from normal at baseline to high at any time (%)

Data on file, Lilly Research Laboratories, ZYP20081112B

*P<.05 versus 150 mg/2 wk

†P<.05 versus 405 mg/4 wk

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(olanzapine) For Extended Release
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Comparison of doses in this study revealed differences on 3 safety parameters: weight, prolactin, and fasting triglycerides, with patients treated with the highest ZYPREXA RELPREVV dose, 300 mg every 2 weeks, experiencing the greatest mean increases in weight and prolactin and also being more likely to experience an increase in triglyceride levels from normal to high.

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Metabolic Monitoring

- **Hyperglycemia, in some cases associated with ketoacidosis, coma or death, has been reported**
 - Olanzapine appears to have a greater association with increases in blood glucose levels than some other atypicals*
 - Monitor patients on olanzapine regularly for worsening of glucose control.
 - Consider the benefits/risks when giving olanzapine to patients with diabetes and to those with borderline hyperglycemia
 - Patients starting treatment with olanzapine should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment
 - Conduct fasting blood glucose testing in patients who develop symptoms of hyperglycemia during treatment

* Relative risk estimates are inconsistent, and the association between atypical antipsychotics and increases in blood glucose appear to fall in a continuum

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ZYPREXA Relprevv
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- Because the active ingredient of ZYPREXA RELPREVV is the same as oral olanzapine, clinicians should follow the same guidance with regard to metabolic changes that they would for the oral formulation.
- Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including olanzapine. Relative risk estimates are inconsistent, and the association between atypical antipsychotics and increases in blood glucose appear to fall in a continuum. Olanzapine appears to have a greater association with increases in blood glucose levels than some other atypicals.
- Patients on olanzapine should be monitored regularly for worsening of glucose control. Benefits and risks of olanzapine should be considered when prescribing the product to patients with diabetes and to those with borderline hyperglycemia.
- Patients starting treatment with olanzapine should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment.
- Fasting blood glucose tests should be conducted in patients who develop symptoms of hyperglycemia during treatment

Metabolic Monitoring

■ Hyperlipidemia

- Undesirable lipid alterations have been observed. Clinical monitoring including baseline and follow-up lipid evaluations is advised
- Clinically significant, sometimes very high, elevations in triglycerides and modest mean increases in total cholesterol have been observed with olanzapine use

■ Weight

- Monitor patient weight regularly during treatment with olanzapine
- Consider potential consequences of weight gain prior to initiating olanzapine

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zyprexaRelprevv
(olanzapine) For Extended Release
Injectable Suspension

- Undesirable lipid alterations have been observed during treatment with olanzapine. Clinical monitoring, including baseline and follow-up lipid evaluations, is advised.
- Clinically significant and sometimes very high elevations in triglycerides have been observed during olanzapine use. Modest mean increases in total cholesterol have also been observed.
- Patients should be monitored regularly for weight gain during treatment with olanzapine. Prescribers should consider the potential consequences of weight gain prior to initiating treatment.

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Post-Injection Delirium/Sedation Syndrome (PDSS) Events in Premarketing Clinical Trials*

- In premarketing ZYPREXA RELPREVV clinical trials:
 - >2000 patients have received ZYPREXA RELPREVV
 - >50,000 injections have been given
 - PDSS events occurred in 0.07% of injections (~1 event per 1400 injections), in approximately 1.7 % of patients*
 - In a clinic with 60 patients given 1 injection every 2 weeks, a 0.07% incidence would suggest that the clinic would see approximately 1 PDSS event per year

A PDSS event can occur in any patient at any injection

* As of 18 June 2009, Data on file, Lilly Research Laboratories, ZYP20081112C

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Zyprexa Relprevv
(olanzapine) For Extended Release
Injectable Suspension

In premarketing clinical trials, an unexpected degree of delirium and/or sedation was reported in a small number of patients with schizophrenia shortly after receiving an injection. This event has been termed Post-injection Delirium/Sedation Syndrome, or PDSS.

Across all ZYPREXA RELPREVV premarketing clinical trials as of 18 June 2009, over 2000 patients have received over 50,000 injections of ZYPREXA RELPREVV. Of these, 0.07% of injections were followed by patients experiencing this temporary post-injection reaction. This incidence corresponds to 1 PDSS event occurring for approximately every 1400 injections. To put this rate into context, in a clinic with 60 patients given 1 injection every 2 weeks, you would expect to see approximately 1 such event per year.

Nevertheless, it is important to be aware that a PDSS event can occur in any patient at any injection.

What is Post-Injection Delirium/Sedation Syndrome?

- Appears related to excessive olanzapine plasma concentrations
- Presentation consistent with many symptoms of oral olanzapine overdose
- Most patients developed symptoms of:
 - *Sedation*, ranging from mild in severity up to coma (lasting up to 12 hrs) and/or
 - *Delirium*, including confusion, disorientation, agitation, anxiety and other cognitive impairment
 - Other symptoms noted included extrapyramidal symptoms, dysarthria, ataxia, aggression, dizziness, weakness, hypertension or convulsions
- Typically began with milder symptoms which progress in severity and/or number
- Presentation can appear similar to alcohol intoxication

Time of Onset of Symptoms	% of Patients*
≤1 hour	~80%
>1 to 3 hours	~ 14%
>3 hours	~ 6%

* As of 18 June 2009.
Data on file, Lilly Research
Laboratories, ZYP20090209A

For complete safety profile, including boxed warnings,
see the full Prescribing Information.

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ZYPREXA Relprevv
(olanzapine) For Extended Release
Injectable Suspension

What is Post-injection Delirium/Sedation Syndrome?

- These events appear to be related to excessive olanzapine plasma concentrations and presentation of the events are consistent with many symptoms of oral olanzapine overdose. While the precise mechanism of these events remains unknown, ZYPREXA RELPREVV is more soluble in blood than in muscle. Contact with a substantial volume of blood would lead to faster dissolution (as the olanzapine disassociates from the pamoic acid), resulting in higher than expected olanzapine concentrations. There are several ways that such contact could occur, including direct or partial injection into the vasculature, blood vessel injury during the injection, or as the result of an extravascular bleed around the vessel.
- Most patients who experienced such an event developed symptoms related to sedation and/or delirium. Sedation could range from mild to severe, and in one case included coma lasting up to 12 hours. Symptoms related to delirium could include confusion, disorientation, agitation, anxiety, and other cognitive impairment. Other symptoms that were noted in some cases included extrapyramidal symptoms, dysarthria, ataxia, aggression, dizziness, weakness, hypertension, or convulsions.
- PDSS events typically began with milder symptoms which then progressed in severity and/or number. The clinical presentation has sometimes been described as appearing similar to that of alcohol intoxication.
- Time after injection to event ranged from soon after injection to greater than 3 hours after injection.

Medical Status and Recovery

- **In patients experiencing Post-Injection Delirium/Sedation Syndrome Events*:**
 - No clinically significant decreases in blood pressure noted
 - No respiratory depression noted
 - Some patients experienced temporary unconsciousness (~ 15%)
 - Most patients were hospitalized for further observation and/or treatment (~ 74%)
 - Two patients were intubated prophylactically following parenteral administration of benzodiazepines (No respiratory depression noted)
 - Concomitant medications/substances have not been shown to be risk factors
- **Recovery in patients experiencing Post-Injection Delirium/Sedation Syndrome Events*:**
 - All patients have largely recovered within 72 hours
 - Approximately 70% of patients chose to continue to receive ZYPREXA RELPREVV injections after experiencing a PDSS event

* As of 18 June 2009. Data on file, Lilly Research Laboratories, ZYP20090209A

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ZYPREXA **Relprevv**
(olanzapine) For Extended Release
Injectable Suspension

There have been no clinically significant decreases in blood pressure and no respiratory depression noted in any of the PDSS events in the premarketing clinical trials. Approximately 15% of cases experienced temporary unconsciousness. In most cases, patients were hospitalized for further observation and/or treatment. Two patients were intubated prophylactically following parenteral administration of benzodiazepines, with no respiratory depression noted. Concomitant medications or substances have not been shown to be risk factors for these events.

It is important to note that all patients who experienced a post-injection syndrome event largely recovered within 72 hours. Time of full recovery has ranged from 1.5 to 72 hours, with full recovery defined as the absence of signs or symptoms of the event. Approximately 70% of these patients chose to continue receiving ZYPREXA RELPREVV following the event.

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Safety Precautions at Every ZYPREXA RELPREVV Injection

- **Before the injection:**
 - For product reconstitution procedure, review the Reconstitution and Administration Poster and the Reconstitution and Administration Training video available on the ZYPREXA RELPREVV Patient Care Program Web site
 - Provide the Medication Guide and answer patient or legal guardian questions prior to each injection
 - **IMPORTANT:** confirm there will be someone to accompany the patient after the 3-hour monitoring period. If this cannot be confirmed, do not give the injection

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ZYPREXA Relprevv
*(olanzapine) For Extended Release
 Injectable Suspension*

Because there is a risk of a PDSS event with each injection, the following precautions should be followed every time a patient receives a ZYPREXA RELPREVV injection. For a description of the product reconstitution and administration procedures, please review the Reconstitution and Administration Poster and training video available on the ZYPREXA RELPREVV Patient Care Program web site.

The Medication Guide must be given to patients, their families or their caregivers prior to each injection. For additional information about ZYPREXA RELPREVV, patients can receive the patient education brochure, Getting Started with My Medicine. Prescribers or other healthcare professionals should instruct patients, their families, and their caregivers to read these documents and should assist them in understanding the contents. Before each injection, patients or legal guardian should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have.

Before administering ZYPREXA RELPREVV, confirm that the patient will be accompanied to their destination (for example to their home or workplace) when they leave the healthcare facility. If this cannot be confirmed, do not give the injection.

Safety Precautions at Every ZYPREXA RELPREVV Injection

- **During the injection:**
 - ZYPREXA RELPREVV is intended for deep intramuscular gluteal injection only
 - Do not administer intravenously or subcutaneously
 - Not approved for deltoid injections
 - Administrator must aspirate the syringe for several seconds prior to injection to ensure no blood is visible
 - Do not proceed with injection if blood is visible in the syringe
 - Discard syringe and use a new vial
 - Reconstitute a new vial and inject into alternate side of buttock, deep into gluteal muscle

For complete safety profile, including boxed warnings, see the full Prescribing Information.

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ZYPREXA Relprevv
(olanzapine) For Extended Release
Injectable Suspension

It is important to note that the risk of a PDSS event is present with each injection of ZYPREXA RELPREVV. Although this risk cannot be eliminated, good injection technique is necessary to minimize the occurrence of these events.

ZYPREXA RELPREVV is intended for deep intramuscular gluteal injection only. Do **not** administer intravenously or subcutaneously. It is **not** approved for deltoid injections.

Administrators must aspirate the syringe for several seconds prior to injection to ensure that no blood is visible in the syringe. If blood **is** visible, they must not proceed with the injection. They should discard the syringe and reconstitute a new vial for injection, then inject into the alternate side of the buttock, deep into the gluteal muscle.

Safety Precautions at Every ZYPREXA RELPREVV Injection

- **After the injection:**

- A healthcare professional must continuously observe the patient at the registered healthcare facility with ready access to emergency response services for at least 3 hours
 - The patient should be located where he/she can be seen and/or heard
 - The 3-hour observation period may be used to conduct other activities, such as psychosocial and psychoeducational programs

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Directly after the injection, patients must be observed by appropriately qualified personnel at the registered healthcare facility with ready access to emergency response services for at least 3 hours. The patient should be located in an area where he or she can be seen and/or heard at all times. The 3-hour observation period may be used to conduct other activities, such as psychosocial or psychoeducational programs.

Safety Precautions at Every ZYPREXA RELPREVV Injection

- **Before patient leaves the healthcare facility:**
 - Confirm that the patient is alert, oriented, and without signs or symptoms of a post-injection delirium/sedation syndrome event. If PDSS is suspected, close medical supervision and monitoring should be instituted in a facility capable of resuscitation
 - Advise patients and caregivers to be vigilant for symptoms of a PDSS event for the remainder of the day and be able to obtain medical assistance if needed
 - All patients must be accompanied to their destination upon leaving the facility
- **After leaving the healthcare facility:**
 - For the remainder of the day of each injection, patients should not drive or operate heavy machinery

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After completion of the observation period and before the patient leaves the healthcare facility, the patient must be confirmed to be alert, oriented, without any signs or symptoms of a PDSS event. If PDSS is suspected, close medical supervision and monitoring should be instituted in a facility capable of resuscitation.

The patient and the caregiver should be advised to be vigilant for appearance of symptoms of a PDSS event for the remainder of the day and should be able to obtain medical assistance if needed. All patients must be accompanied to their destination upon leaving the facility.

Patients should also be cautioned that after leaving the facility, they should not drive or operate heavy machinery for the remainder of the day.

Clinical Management of PDSS Events

- **Patients experiencing PDSS should be managed as clinically appropriate**
 - If post-injection delirium/sedation syndrome is suspected, close medical supervision and monitoring should be instituted in a facility capable of resuscitation
 - Patients may be treated symptomatically
 - If parenteral benzodiazepines are required for patient management during a PDSS event, careful evaluation of clinical status for excessive sedation and cardiorespiratory depression is recommended
 - If the patient is sent to a hospital for further observation and/or management, it is recommended that the prescribing healthcare professional notify the hospital personnel that the patient is experiencing a probable olanzapine overdose following injection of ZYPREXA RELPREVV

Report any suspected PDSS event within 24 hours through the ZYPREXA RELPREVV Patient Care Program

For complete safety profile, including boxed warnings, see the full Prescribing Information.

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ZYPREXA Relprevv
(olanzapine) For Extended Release
Injectable Suspension

What should be done if a patient experiences a post-injection syndrome event?

- There is no specific antidote for olanzapine overdose. Patients experiencing PDSS should be managed as clinically appropriate and may be treated symptomatically in a facility capable of resuscitation.
- If parenteral benzodiazepines are required for patient management during a PDSS event, careful evaluation of clinical status for excessive sedation and cardiorespiratory depression is recommended.
- If the patient is sent to a hospital for further observation and/or management, it is recommended that the prescribing healthcare professional notify the hospital personnel that the patient is experiencing a probable olanzapine overdose following injection of ZYPREXA RELPREVV.
- **It is very important that you report any suspected PDSS event through the ZYPREXA RELPREVV Patient Care Program within 24 hours of becoming aware of the event.**

Clinical Management Following PDSS Events

Following a PDSS event

- **If treatment with ZYPREXA RELPREVV is continued:**
 - The next injection may occur as previously scheduled, or earlier if clinically indicated for exacerbation of symptoms
 - Temporary oral supplementation may be considered
- **If ZYPREXA RELPREVV is discontinued:**
 - The effects of ZYPREXA RELPREVV will continue for some time after discontinuation
 - Treatment with alternative medication may be started when clinically indicated

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ZYPREXA Relprevv
(olanzapine) For Extended Release
Injectable Suspension

In clinical trials, after a PDSS event, approximately 70% of patients elected to continue to receive ZYPREXA RELPREVV and were dosed at their next regularly scheduled visit.

If the healthcare professional and patient decide to continue treatment with ZYPREXA RELPREVV following a PDSS event, the next injection may occur as previously scheduled. Dosing and/or oral supplementation should be managed as clinically indicated.

If ZYPREXA RELPREVV is discontinued following a PDSS event, the healthcare professional should be aware that, as with all long-acting medications, the effects of ZYPREXA RELPREVV will continue for some time after discontinuation of the drug. Treatment with alternative medication may be started when clinically indicated.

ZYPREXA RELPREVV Patient Care Program

- **ZYPREXA RELPREVV is available only through a controlled distribution system to registered prescribers for use in registered facilities**
- **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:**
 - 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;
 - 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
 - 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.

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ZYPREXARelprevv
(olanzapine) For Extended Release
Injectable Suspension

ZYPREXA RELPREVV is available only through a controlled distribution system to registered prescribers for use in registered facilities. Participation in the ZYPREXA RELPREVV Patient Care Program is mandatory for patients, prescribers, healthcare facilities and pharmacy service providers.

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:

- 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;
- 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
- 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.

Required Enrollments

- In order to use ZYPREXA RELPREVV, all of the following must be enrolled in the ZYPREXA RELPREVV Patient Care Program:
 - Prescriber
 - Healthcare facility or program
 - Patient
 - Pharmacy service provider
- Only patients who are enrolled in the ZYPREXA RELPREVV Patient Care Program may receive ZYPREXA RELPREVV injections

For detailed enrollment information, refer to the ZYPREXA RELPREVV Patient Care Program Website at www.zyprexarelprevvprogram.com or call 877-772-9390

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Much like other programs, enrollment is required for the prescriber, patient, and pharmacy.

In addition, a unique component of the ZYPREXA RELPREVV Patient Care Program is that the healthcare facility or program will also be required to be enrolled in the ZYPREXA RELPREVV Patient Care Program. These requirements will be described next.

Detailed information on all required enrollments is available by accessing the ZYPREXA RELPREVV Patient Care Program Web site or calling 877-772-9390.

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Prescriber Registration

All prescribers who intend to prescribe ZYPREXA RELPREVV must enroll in the ZYPREXA RELPREVV Patient Care Program prior to treating any patient with ZYPREXA RELPREVV

■ **Prescriber obligations include:**

- Completing the mandatory ZYPREXA RELPREVV training
- Understanding the ZYPREXA RELPREVV Patient Care Program requirements and the risks associated with ZYPREXA RELPREVV
- Understanding the clinical presentation of PDSS and how to manage patients should an event occur while using ZYPREXA RELPREVV
- Understanding 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
- Initiating ZYPREXA RELPREVV only in patients for whom tolerability with oral olanzapine has been established
- Reviewing the ZYPREXA RELPREVV Medication Guide with each patient or legal guardian prior to prescribing
- Ensuring that all patients are enrolled in the ZYPREXA RELPREVV Patient Care Program registry prior to prescribing ZYPREXA RELPREVV by completing the Patient Registration Form
- Ensuring all suspected cases of PDSS are reported to the ZYPREXA RELPREVV Patient Care Program within 24 hours of becoming aware of the event
- Agreeing to be contacted by the ZYPREXA RELPREVV Patient Care Program coordinating center to resolve discrepancies, to obtain information about a patient, or to conduct occasional surveys

For complete safety profile, including boxed warnings, see the full Prescribing Information.

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All prescribers who intend to prescribe ZYPREXA RELPREVV must enroll in the ZYPREXA RELPREVV Patient Care Program prior to treating any patient with ZYPREXA RELPREVV.

Prescriber obligations include:

- Completing the mandatory ZYPREXA RELPREVV training
- Understanding the ZYPREXA RELPREVV Patient Care Program requirements and the risks associated with ZYPREXA RELPREVV
- Understanding the clinical presentation of PDSS and how to manage patients should an event occur while using ZYPREXA RELPREVV
- Understanding 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
- Initiating ZYPREXA RELPREVV only in patients for whom tolerability with oral olanzapine has been established
- Reviewing the ZYPREXA RELPREVV Medication Guide with each patient or legal guardian prior to prescribing
- Ensuring that all patients are enrolled in the ZYPREXA RELPREVV Patient Care Program registry prior to prescribing ZYPREXA RELPREVV by completing the Patient Registration Form
- Ensuring all suspected cases of PDSS are reported to the ZYPREXA RELPREVV Patient Care Program within 24 hours of becoming aware of the event
- Agreeing to be contacted by the ZYPREXA RELPREVV Patient Care Program coordinating center to resolve discrepancies, to obtain information about a patient, or to conduct occasional surveys

Patient Registration

All patients who are treated with ZYPREXA RELPREVV must be enrolled in the ZYPREXA RELPREVV Patient Care Program prior to receiving their first ZYPREXA RELPREVV injections

- Enrollment includes signed patient attestation of understanding of the ZYPREXA RELPREVV Patient Care Program data collection requirements, ZYPREXA RELPREVV's risks and benefits, and the special precautions which safe use of the product mandate.
- If a patient is unable to provide attestation, his/her legal guardian will consult with the prescriber and provide attestation for the patient
- In situations where a patient is under a court order for involuntary psychiatric treatment which permits administration of medications without patient consent, patient signature can be omitted. However, check the appropriate box and provide the expiration date for the Court Order.

For complete safety profile, including boxed warnings, see the full Prescribing Information.

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ZYPREXA Relprevv
(olanzapine) For Extended Release
Injectable Suspension

All patients who are treated ZYPREXA RELPREVV must be enrolled in the ZYPREXA RELPREVV Patient Care Program prior to receiving their first ZYPREXA RELPREVV injection.

- Enrollment includes signed patient attestation of understanding of the ZYPREXA RELPREVV Patient Care Program data collection requirements, ZYPREXA RELPREVV's risks and benefits, and the special precautions mandated for safe use of the product.
- If a patient is unable to provide attestation, his/her legal guardian will consult with the prescriber and provide attestation for the patient.
- In situations where a patient is under a court order for involuntary psychiatric treatment which permits administration of medications without patient consent, patient signature can be omitted. However, check the appropriate box and provide the expiration date for the Court Order.

Healthcare Facility or Program Registration

The healthcare facility where a patient will receive the injection of ZYPREXA RELPREVV must also enroll in the ZYPREXA RELPREVV Patient Care Program prior to any patients being enrolled

■ **Healthcare facility obligations include:**

- Ensuring that all appropriate staff are trained and have read and understand the ZYPREXA RELPREVV Patient Care Program Instructions Brochure as well as the Training Materials
- Ensuring 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
- Ensuring the facility 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
- Ensuring 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
- Ensuring that the Medication Guide is provided to the patient or legal guardian prior to each injection
- Ensuring that the appropriate staff monitors the patient continuously for at least 3 hours
- Ensuring that required data are submitted within 7 days after each injection to the ZYPREXA RELPREVV Patient Care Program
- Understanding the facility may be contacted by the ZYPREXA RELPREVV Patient Care Program Coordinating Center to clarify information provided or obtain information about the patient

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ZYPREXA Relprevv
(olanzapine) For Extended Release
Injectable Suspension

The healthcare facility where a patient will receive the injection of ZYPREXA RELPREVV must also enroll in the ZYPREXA RELPREVV Patient Care Program prior to any patients being enrolled.

Healthcare facility obligations include:

- Ensuring that all appropriate staff are trained and have read and understand the ZYPREXA RELPREVV Patient Care Program Instructions Brochure as well as the Training Materials
- Ensuring 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
- Ensuring the facility 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
- Ensuring 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
- Ensuring that the Medication Guide is provided to the patient or legal guardian prior to each injection
- Ensuring that the appropriate staff monitors the patient continuously for at least 3 hours
- Ensuring that required data are submitted within 7 days after each injection to the ZYPREXA RELPREVV Patient Care Program
- Understanding the facility may be contacted by the ZYPREXA RELPREVV Patient Care Program Coordinating Center to clarify information provided or obtain information about the patient

Pharmacy Service Provider Registration

All pharmacy service providers that intend to order and dispense ZYPREXA RELPREVV must enroll in the ZYPREXA RELPREVV Patient Care Program and agree to comply with the program including data collection, confirmation of eligible prescribers and patients prior to dispensing, and program reporting requirements

▪ **Pharmacy Service Provider obligations include:**

- Ensuring that all appropriate pharmacy staff are trained and have read and understand the ZYPREXA RELPREVV Patient Care Program Instructions Brochure
- Ensuring 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
- Ensuring 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
- Ensuring that pharmacy staff will not dispense ZYPREXA RELPREVV directly to patients
- Ensuring that pharmacy staff report the date of each ZYPREXA RELPREVV dispensing to the ZYPREXA RELPREVV Patient Care Program
- Understanding that the pharmacy may be contacted by the ZYPREXA RELPREVV Patient Care Program to clarify information provided or to obtain information about a patient

For complete safety profile, including boxed warnings, see the full Prescribing Information.

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ZYPREXA Relprevv
(olanzapine) For Extended Release
Injectable Suspension

All pharmacy service providers that intend to order and dispense ZYPREXA RELPREVV must enroll in the ZYPREXA RELPREVV Patient Care Program and agree to comply with the program including data collection, confirmation of eligible prescribers and patients prior to dispensing, and program reporting requirements.

Pharmacy Service Provider obligations include:

- Ensuring that all appropriate pharmacy staff are trained and have read and understand the ZYPREXA RELPREVV Patient Care Program Instructions Brochure
- Ensuring 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
- Ensuring 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
- Ensuring that pharmacy staff will not dispense ZYPREXA RELPREVV directly to patients
- Ensuring that pharmacy staff report the date of each ZYPREXA RELPREVV dispensing to the ZYPREXA RELPREVV Patient Care Program
- Understanding that the pharmacy may be contacted by the ZYPREXA RELPREVV Patient Care Program to clarify information provided or to obtain information about a patient

Training Summary

After this training, you should now be able to:

- ✓ Differentiate between ZYPREXA RELPREVV (olanzapine for extended release injectable suspension) and ZYPREXA IntraMuscular (olanzapine for injection) to avoid medication errors
- ✓ Understand the dosing options with ZYPREXA RELPREVV
- ✓ Know the common adverse events associated with ZYPREXA RELPREVV and how to monitor patients for metabolic changes
- ✓ Identify a post-injection delirium/sedation syndrome (PDSS) event in your clinical practice
- ✓ Know the conditions of safe use and how to manage the risk of PDSS
- ✓ Know what to do in case a PDSS event occurs
- ✓ Understand basics of the ZYPREXA RELPREVV Patient Care Program

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For complete safety profile, including boxed warnings, see the full Prescribing Information.

Version 2.0 03-Aug-2012

ZYPREXA *Relprevv*
(olanzapine) For Extended Release
Injectable Suspension

After this training, you should now be able to:

- Differentiate between ZYPREXA RELPREVV (olanzapine for extended release injectable suspension) and ZYPREXA IntraMuscular (olanzapine for injection) to avoid medication errors,
- Understand the dosing options with ZYPREXA RELPREVV.
- Know the common adverse events associated with ZYPREXA RELPREVV and how to monitor for metabolic changes
- Identify a post-injection delirium/sedation syndrome event in your clinical practice,
- Know the conditions of safe use and how to manage the risk of post-injection delirium/sedation syndrome
- Know what to do in case a post-injection delirium/sedation syndrome event occurs.
- And finally, understand the basics of the ZYPREXA RELPREVV Patient Care Program.

ZYPREXA[®]Relprevv[™]

(olanzapine) For Extended Release
Injectable Suspension



Please see Prescribing Information for full details about the risks of ZYPREXA RELPREVV, including Boxed Warnings.



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ZYPREXA RELPREVV Prescribing Information and Medication Guide Patient Injection and PDSS Reporting Forms

- ▶ **Single Patient Injection Form**
 - Used to collect the data for a single patient after treatment administration of ZYPREXA RELPREVV.
 - This form is to be sent to the ZYPREXA RELPREVV Patient Care Program Coordinating Center within 7 days after the patient's injection.
- ▶ **Multiple Patient Injection Form**
 - Used when injections are administered to multiple patients on the same day at a given facility. This form is used to collect the data for multiple patients after treatment administration of ZYPREXA RELPREVV.
 - This form is to be sent to the ZYPREXA RELPREVV Patient Care Program Coordinating Center within 7 days after the patients' injections.
- ▶ **Post-Injection Delirium/Sedation Syndrome (PDSS) Form**
 - This form is used to collect the required data when a suspected PDSS event occurs after administration of ZYPREXA RELPREVV, either during the 3-hour observation period or any time thereafter. This form must be provided to the ZYPREXA RELPREVV Patient Care Program Coordinating Center within 24 hours of becoming aware of a suspected PDSS event.

Enclosed Registration Forms Include:

- ▶ **Prescriber Registration**
 - Enrolls the prescriber to treat patients with ZYPREXA RELPREVV.
- ▶ **Pharmacy Service Providers**
 - **Pharmacy Registration**
 - Enrolls the pharmacy to order and dispense ZYPREXA RELPREVV.
 - **Buy and Bill Pharmacy Service Provider Registration**
 - For prescribers who get product through standard buy and bill procedures, this form enrolls the prescriber as a Pharmacy Service Provider. **NOTE: Prescribers intending to buy and bill must complete both the Prescriber and Buy and Bill Pharmacy Service Provider Registration Forms.**
- ▶ **Patient Registration**
 - Enrolls the patient to receive treatment with ZYPREXA RELPREVV.
- ▶ **Patient Registration Form – Patient Copy**
 - Provides patient or caregiver a copy of attestations from the Patient Registration Form.
- ▶ **Healthcare Facility Registration**
 - Enrolls the healthcare facility to administer ZYPREXA RELPREVV injections and monitor patients after each injection.

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Introduction to the ZYPREXA RELPREVV Patient Care Program

Patient Care Program Overview

ZYPREXA RELPREVV is the long-acting intramuscular formulation of olanzapine indicated for treatment of schizophrenia. The ZYPREXA RELPREVV Patient Care Program is a Risk Evaluation and Mitigation Strategy (REMS) program necessary to mitigate the risk of negative outcomes associated with ZYPREXA RELPREVV post-injection delirium/sedation syndrome (PDSS). In order to prescribe, dispense, receive, or administer ZYPREXA RELPREVV, healthcare professionals need to:

- Enroll in the ZYPREXA RELPREVV Patient Care Program
- Ensure the collection of information for each injection of ZYPREXA RELPREVV

Post-Injection Delirium/Sedation Syndrome:

ZYPREXA RELPREVV has been associated with a post-injection delirium/sedation syndrome characterized primarily by signs and symptoms consistent with olanzapine overdose. This syndrome does not apply to any other formulation of olanzapine, including ZYPREXA IntraMuscular (olanzapine for injection). The prescribing information for ZYPREXA RELPREVV includes the following BOXED WARNING.

BOXED WARNING

See full prescribing information and the healthcare professional training for complete information on PDSS.

Post-Injection Delirium/Sedation Syndrome — Adverse events with signs and symptoms consistent with olanzapine overdose, in particular, sedation (including coma) and/or delirium, have been reported following injections of ZYPREXA RELPREVV. ZYPREXA RELPREVV must be administered in a registered healthcare facility with ready access to emergency response services. After each injection, patients must be observed at the healthcare facility by a healthcare professional for at least 3 hours. Because of this risk, ZYPREXA RELPREVV is available only through a restricted distribution program called ZYPREXA RELPREVV Patient Care Program and requires prescriber, healthcare facility, patient, and pharmacy enrollment.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis — Elderly patients with dementia related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. ZYPREXA RELPREVV is not approved for the treatment of patients with dementia-related psychosis.

ZYPREXA RELPREVV™
(olanzapine) For Extended Release
Injectable Suspension

ZYPREXA RELPREVV Patient Care Program Enrollment

Prescriber

- Reviews educational materials
- Submits enrollment form to ZYPREXA RELPREVV Patient Care Program Coordinating Center

Healthcare Facility

- Ensures staff are trained and facility can comply with conditions of safe use
- Submits enrollment form to ZYPREXA RELPREVV Patient Care Program Coordinating Center
- Receives & stores patient authorization notification

Patient

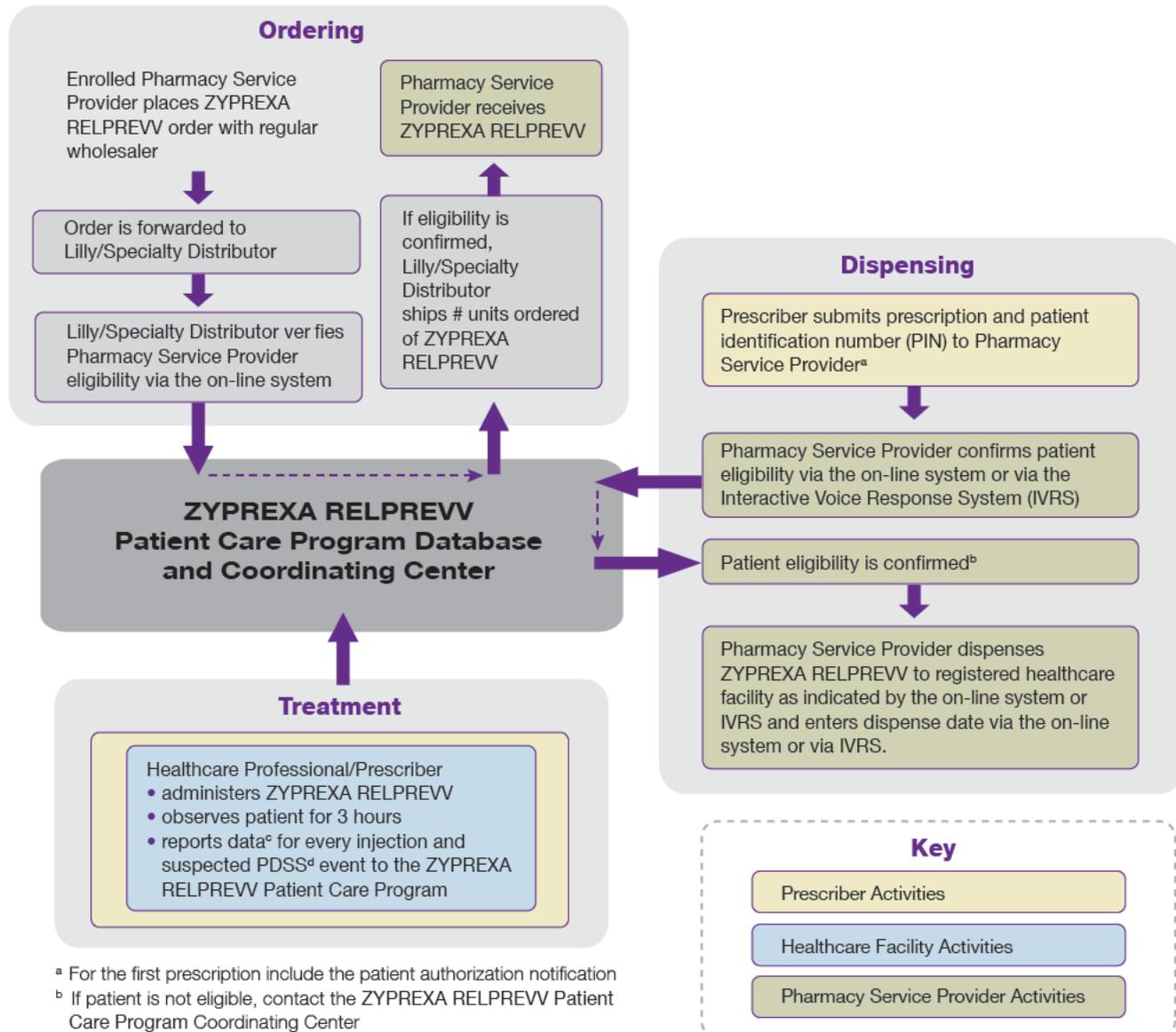
To enroll patient, prescriber:

- Reviews risks of ZYPREXA RELPREVV with patient
- Obtain signature of patient or legal guardian OR check box if court order of involuntary commitment
- Submits enrollment form to ZYPREXA RELPREVV Patient Care Program Coordinating Center
- Receives & stores patient authorization notification

Pharmacy Service Provider

- Reviews ZYPREXA RELPREVV Patient Care Program materials
- Ensures pharmacy staff are trained
- Submits enrollment form to ZYPREXA RELPREVV Patient Care Program Coordinating Center

ZYPREXA RELPREVV Patient Care Program Process Flow



^a For the first prescription include the patient authorization notification

^b If patient is not eligible, contact the ZYPREXA RELPREVV Patient Care Program Coordinating Center

^c Data entry is required for patient to be eligible for refill

^d PDSS = post-injection delirium/sedation syndrome

ZYPREXA RELPREVV Patient Care Program Coordinating Center Contact Information

For questions regarding the Patient Care Program or to enroll, please contact the Patient Care Program Coordinating Center:

Via Telephone: 1-877-772-9390
Monday – Friday: 8:00am – 8:00pm ET

Via Mail: ZYPREXA RELPREVV Patient Care Program
P.O. Box 4649
Star City, WV 26504-4649

Via Fax: 1-877-772-9391

Via Internet: www.zyprexarelprevvprogram.com

Prescriber Information

Prescribers must enroll in the ZYPREXA RELPREVV Patient Care Program in order to prescribe ZYPREXA RELPREVV.

Three Steps to Prescriber Enrollment:

1. Review:

Attend a training or review the following educational materials:

- ZYPREXA RELPREVV Patient Care Program Instructions Brochure (this document)
- Healthcare Professional Training Slide Presentation with text notes or Recorded Presentation with participant guide, available at www.zyprexarelprevvprogram.com

2. Complete/Sign:

Complete the Prescriber Registration Form on-line, or print and sign.

3. Submit:

Submit on-line or via fax or mail to the Patient Care Program Coordinating Center.

Prescribers must repeat the enrollment process every 3 years. You will be notified by fax or email 60 days prior to your reenrollment date.

Enrolling in the ZYPREXA RELPREVV Patient Care Program will allow prescribers to securely and easily view data for all of the patients they have enrolled in the program, along with the patients' next expected injection dates and injection histories.

Upon registration, the prescriber will be sent a username and password, which allows secured access to the on-line Patient Care Program system. The prescriber is responsible for entering required Patient Care Program data for any PDSS event that occurs.

Prescribers who obtain ZYPREXA RELPREVV through a pharmacy: Provide a prescription to a registered pharmacy.

Prescribers who order and dispense ZYPREXA RELPREVV through buy and bill procedures: Enroll as a Buy and Bill Pharmacy Service Provider as described on pages 9 and 10 of this brochure.

The facility/practice where injections are administered or patients are monitored must be enrolled in the ZYPREXA RELPREVV Patient Care Program as a healthcare facility as described on page 7. The Prescriber will receive an email or fax notification once the healthcare facility(s) become enrolled. The healthcare facility(s) are required to enter data following each patient injection.

Prescriber Information

To report SUSPECTED ADVERSE REACTIONS other than PDSS, contact Eli Lilly and Company at 1-800-LILLYRX (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

The prescriber is responsible for enrolling the **patient** in the ZYPREXA RELPREVV Patient Care Program prior to writing a prescription for that patient.

Three Steps to Patient Enrollment:

1. Confirm:

- Both the prescriber and the healthcare facility where the patient will receive the injection are enrolled in the ZYPREXA RELPREVV Patient Care Program.
- Patient has been provided with a Medication Guide and informed about the risks associated with the administration of ZYPREXA RELPREVV.
- Patient has been informed about the Patient Care Program guidelines.

2. Complete/Sign:

Complete a Patient Registration Form and have the patient or legal guardian sign the form, or check the box relating to the presence of a court order. If the court order box is checked, provide the expiration date of the court order. Provide the Patient Registration Form-Patient Copy version to the patient or legal guardian.

3. Submit:

Submit on-line or via fax or mail to the Patient Care Program Coordinating Center.

After enrollment is complete, a unique Patient Identification Number (PIN) and a healthcare facility unique identifier will be provided to the prescriber via a patient authorization notification fax or email.

The prescriber should provide the patient's PIN and healthcare facility unique identifier with the first prescription to assist the pharmacy service provider in completing its ZYPREXA RELPREVV Patient Care Program responsibilities.

For any changes in patient care setting, changes in prescriber, or to discontinue or reactivate a patient, call the Coordinating Center (1-877-772-9390).

Patient Care Program Data Entry

All suspected cases of PDSS should be reported to the ZYPREXA RELPREVV Patient Care Program within **24 hours of awareness of the event**. The ZYPREXA RELPREVV Patient Care Program may need to contact you to obtain additional information to further characterize the PDSS event.

For each suspected PDSS event, the prescriber can record and submit data to the Patient Care Program in one of the following ways:

Via Telephone: 1-877-772-9390

Via Fax: 1-877-772-9391

Via Internet: www.zyprexarelprevvprogram.com

Steps for On-line Data Entry

1. With the assigned username and password, log in to the ZYPREXA RELPREVV Patient Care Program system through the website.
2. Upon logging into the Patient Care Program system, the prescriber will see only their associated patients and the option to enroll new patients.
3. Select:
 - The appropriate patient for whom he/she is entering data.
 - Or the option to enroll a new patient.
4. The system will prompt the prescriber to enter enrollment data for a new patient, or PDSS data for an already enrolled patient.

Healthcare Facility Information

A healthcare facility must be enrolled in the ZYPREXA RELPREVV Patient Care Program to: ensure each patient is enrolled in the Patient Care Program prior to administering an injection, to administer ZYPREXA RELPREVV and/or to monitor patients who have been administered ZYPREXA RELPREVV and to enter data for each injection administered to a patient.

Authorized Healthcare Facility Representative

The authorized healthcare facility representative must ensure that all appropriate staff responsible for administering ZYPREXA RELPREVV and for monitoring patients are educated on ZYPREXA RELPREVV injection techniques, signs and symptoms of PDSS, and patient monitoring requirements following

injection. Additionally, the authorized healthcare facility representative is responsible to ensure systems are in place to report all PDSS events to the prescriber and to identify all appropriate staff as delegates who will be responsible for entering data following each injection.

Patient Care Program Data Entry

The authorized healthcare facility representative may assign the Patient Care Program responsibilities to a delegate(s). Upon registration, the delegate(s) will be sent a username and password, which allows secured access to the on-line Patient Care Program system. After registration, additional delegates may be assigned by calling the Coordinating Center (1-877-772-9390).

Three Steps to Healthcare Facility Enrollment:

1. Review:

Staff involved with ZYPREXA RELPREVV patients review the educational materials listed below. Materials are available on-line, through an on-line order form, or by calling the ZYPREXA RELPREVV Patient Care Program Coordinating Center.

- Required for nurse or other individuals giving injections:
 - ZYPREXA RELPREVV Patient Care Program Instructions Brochure (this document)
 - Healthcare Professional Training Slide Presentation with text notes or Recorded Presentation with participant guide, available at www.zyprexarelprevvprogram.com
 - Reconstitution & Administration Training Video and Poster

- Required for staff working with patients post-injection:
 - Healthcare Professional Training Slide Presentation with text notes or Recorded Presentation
 - ZYPREXA RELPREVV Patient Care Program Instructions Brochure (this document)

2. Complete/Sign:

Healthcare facility representative completes the Healthcare Registration Form on-line or print and sign.

3. Submit:

Submit on-line or via fax or mail to the ZYPREXA RELPREVV Patient Care Program Coordinating Center.

Healthcare facilities must repeat the enrollment process every 3 years. You will be notified by fax or email 60 days prior to your reenrollment date.

Healthcare Facility Information

After a patient associated with your facility is enrolled by a prescriber, a unique Patient Identification Number (PIN) will be assigned to the patient and provided to the facility via a patient authorization notification fax or email, which should be filed in the patient's chart.

Prior to each injection, verify that the patient is enrolled in the Zyprexa Relprevv Patient Care Program registry by accessing the system.

Following the injection, patients are to be monitored continuously for at least 3 hours. Report required Patient Care Program injection data (see Injection Form) **within 7 days of injection administration.**

Injection data may be submitted individually for each patient by using the Single Patient Injection Form or for multiple patients by using the Multiple Patient Injection Form.

For each injection, record and submit injection data to the Patient Care Program in one of the following ways:

Via Telephone: 1-877-772-9390

Via Fax: 1-877-772-9391

Via Internet: www.zyprexarelprevvprogram.com

Steps for On-line Data Entry

1. With the assigned username and password, log in to the ZYPREXA RELPREVV Patient Care Program system through the website.
2. Upon logging into the Patient Care Program system, the delegate will see only their associated patients.
3. Select the appropriate patient and dispense date to enter injection data.
4. The system will prompt the delegate to enter injection data for an enrolled patient.

Product Replacement

If, during the course of reconstitution or administration of ZYPREXA RELPREVV, the medication becomes unusable (e.g., aspiration of blood or a broken vial), call the Coordinating Center.

Pharmacy Service Provider Information

A pharmacy service provider must be enrolled in the ZYPREXA RELPREVV Patient Care Program to order and dispense ZYPREXA RELPREVV. Pharmacy service providers include any retail pharmacy, hospital pharmacy, physician or healthcare facility that can order and dispense ZYPREXA RELPREVV.

Three Steps to Pharmacy Service Provider Enrollment:

1. Review:

Pharmacy staff should review the training and education material within this document before dispensing the medication.

2. Complete:

Representative for the pharmacy service provider completes a registration form, depending upon the type of pharmacy operation.

- Pharmacy Registration Form: Enrolls a pharmacy to allow ordering and dispensing of ZYPREXA RELPREVV. To be completed by the pharmacist in charge.
- Buy and Bill Pharmacy Service Provider Registration Form: Enrolls a prescriber organization that wishes to order and dispense ZYPREXA RELPREVV to patients through buy and bill procedures.

3. Submit:

Submit on-line or via fax or mail to the ZYPREXA RELPREVV Patient Care Program Coordinating Center.

Pharmacy Service Providers must repeat the enrollment process every 3 years. You will be notified by fax or email 60 days prior to your reenrollment date.

Once the ZYPREXA RELPREVV Patient Care Program Coordinating Center receives the completed registration form, the pharmacy service provider will be sent a username and password, which allows secured access to the on-line Patient Care Program system and interactive voice response system (IVRS).

Ordering ZYPREXA RELPREVV

ZYPREXA RELPREVV will be shipped through a controlled distribution system. Following the pharmacy service provider registration, the Patient Care Program Coordinating Center will notify distributors that the pharmacy is enrolled. The pharmacy will then be able to submit orders for ZYPREXA RELPREVV to their regular wholesaler.

Patient Care Program requirements must be followed for the pharmacy to maintain an active registration status and to have continued access to ZYPREXA RELPREVV.

Dispensing ZYPREXA RELPREVV

It is the responsibility of the pharmacy service provider to verify the ongoing eligibility of the patient prior to dispensing each prescription and entering the date of each dispensing. The pharmacist will ensure prescription verification (including patient eligibility check and recording the dispense date) is completed on the date of dispense, **prior to** the convenience kit leaving the pharmacy. This is accomplished by contacting the Patient Care Program in one of the following ways:

Via Telephone/IVRS: 1-877-772-9390

Via Internet: www.zyprexareprevvprogram.com

Prior to dispensing ZYPREXA RELPREVV, the pharmacy service provider must confirm that the prescriber, healthcare facility, and patient are enrolled in the ZYPREXA RELPREVV Patient Care Program and that the patient is eligible to receive ZYPREXA RELPREVV via the process outlined below. **The pharmacy service provider must only dispense ZYPREXA RELPREVV to registered healthcare facilities or a healthcare professional, not directly to a patient.**

A patient identification number (PIN) and healthcare facility unique identifier should be provided by the prescriber with the first prescription. Through the on-line Patient Care Program system, the PIN will quickly identify the patient and prescriber as enrolled in the Patient Care Program. The healthcare facility unique identifier will allow confirmation of healthcare facility registration. The system will indicate the patient's eligibility to receive a dispensing of ZYPREXA RELPREVV.

Pharmacy Service Provider Information

Patient eligibility is determined by enrollment in the Patient Care Program and entry of required injection data into the Patient Care Program system by the healthcare facility.

Steps to Dispense:

1. Order the product from a distributor.
2. Receive ZYPREXA RELPREVV from distributor and maintain a supply of product at the pharmacy.
3. Receive a valid prescription, patient identification number (PIN), and healthcare facility unique identifier.
4. Maintain the PIN and healthcare facility unique identifier in the patient record within the pharmacy system to access when refilling a prescription.
5. With the assigned username and password, access the ZYPREXA RELPREVV Patient Care Program system in one of three ways: access the website or call the Coordinating Center (1-877-772-9390) and chose either the Interactive Voice Response System (IVRS) option or speak to a Patient Care Program representative.

Web based – www.zyprexarelprevvprogram.com

- Enter the PIN (If the PIN is not provided, call the Coordinating Center and provide patient's first and last name, patient's date of birth and prescriber's name).
- System displays prescriber and patient name
- Confirm both names match prescription
- System displays healthcare facility number and name
- Confirm healthcare facility name/unique identifier matches patient authorization notification
- The system will indicate the patient's eligibility to receive ZYPREXA RELPREVV.

- If eligible, the pharmacist will enter the date of dispensing (**prior to** the convenience kit leaving the pharmacy) into the Patient Care Program system and dispense only to the healthcare facility (representative) associated with that patient. Do NOT dispense directly to a patient.
- If ineligible, do NOT dispense product. Contact the Patient Care Program Coordinating Center for resolution.

Interactive Voice Response System – call 1-877-772-9390

- Enter the PIN (If the PIN is not provided, call the Coordinating Center and provide patient's first and last name, patient's date of birth and prescriber's name).
- IVRS provides first 5 letters of prescriber and patient last name
- Confirm both names match prescription
- IVRS provides healthcare facility unique identifier
- Confirm unique identifier/healthcare facility name matches patient authorization notification
- The system will indicate the patient's eligibility to receive ZYPREXA RELPREVV.
- If eligible, the pharmacist will enter the date of dispensing (**prior to** the convenience kit leaving the pharmacy) into the Patient Care Program system and dispense only to the healthcare facility (representative) associated with that patient. Do NOT dispense directly to a patient.
- If ineligible, do NOT dispense product. Contact the Patient Care Program Coordinating Center for resolution.

Pharmacy Service Provider Information

Call the Coordinating Center Help Desk 1-877-772-9390

- Provide the PIN (If the PIN is not available, provide patient's first and last name, patient's date of birth and prescriber's name).
- Patient Care Program representative will ask pharmacy provider questions and provides verification of patient eligibility to receive ZYPREXA RELPREVV.
 - If eligible, Patient Care Program representative will enter the date of dispensing **prior to** the convenience kit leaving the pharmacy.
 - Pharmacy Service Provider agrees to dispense only to the healthcare facility (representative) associated with that patient and not directly to a patient.
 - If ineligible, Do NOT dispense product. The Coordinating Center will work to resolve.

Product Replacement

If, during the course of administering a ZYPREXA RELPREVV injection to a patient, an accident occurs that causes the ZYPREXA RELPREVV vial to be broken or to become unusable (e.g., aspiration of blood), call the Coordinating Center.

Reconciliation

Shipping records will be monitored against dispensing data by the Patient Care Program. If dispensing data are not provided, the pharmacy service provider will be contacted to obtain the information. Unreconciled discrepancies may lead to removal of the pharmacy from the approved list of pharmacies for ZYPREXA RELPREVV.

Glossary of Terms

Healthcare Facility

A healthcare facility administering and/or monitoring injections of ZYPREXA RELPREVV.

Interactive Voice Response System (IVRS)

System that allows a pharmacy service provider to confirm patient and prescriber eligibility and provide dispensing data via telephone rather than the on-line system.

Patient Authorization Notification

Provided to the prescriber and healthcare facility upon registration and includes the PIN and healthcare facility unique identifier. To be provided to the pharmacy service provider with the first prescription for each patient.

Patient Identification Numbers (PIN)

Unique numbers assigned to patients, which are used by the pharmacy service provider to confirm enrollment in the ZYPREXA RELPREVV Patient Care Program.

Pharmacy Service Provider

Any retail pharmacy, hospital pharmacy, physician, or properly licensed healthcare facility that can order for and deliver ZYPREXA RELPREVV to a healthcare professional in accordance with their agreement to implement all relevant requirements of the ZYPREXA RELPREVV Patient Care Program.

- Pharmacy - Retail and hospital pharmacies
- Buy & Bill Pharmacy Service Provider – a licensed healthcare provider that purchases pharmaceuticals through a licensed distributor for its own use in the treatment of a patient and then includes the cost of the pharmaceutical in its billing of patients and third-party payers.

Post-Injection Delirium/Sedation Syndrome (PDSS)

During premarketing clinical studies, adverse events that presented with signs and symptoms consistent with olanzapine overdose, in particular, sedation (including coma) and/or delirium, were reported in patients following an injection of ZYPREXA RELPREVV. Sedation ranged from mild in severity to coma and delirium included confusion, disorientation, agitation, anxiety, and other cognitive impairment. Other symptoms noted include extrapyramidal symptoms, dysarthria, ataxia, aggression, dizziness, weakness, hypertension, and convulsion. The potential for onset of the event is greatest within the first hour. The majority of cases have occurred within the first 3 hours after injection; however, the event has occurred after 3 hours.

Prescriber

A healthcare professional writing prescriptions for ZYPREXA RELPREVV. Prescribers are responsible for ensuring that all patients receiving ZYPREXA RELPREVV are enrolled in the program.

BUY & BILL* PHARMACY SERVICE PROVIDER REGISTRATION FORM

BUY & BILL
PHARMACY



To be enrolled in the ZYPREXA RELPREVV Patient Care Program, complete and fax this form to 1-877-772-9391.

Training must be completed before a pharmacy service provider may be enrolled in the ZYPREXA RELPREVV Patient Care Program.

PHARMACY SERVICE PROVIDER INFORMATION

Enrollment Reenrollment

Facility Name: _____

DEA Number: _____

Please specify description of Pharmacy: Community/Retail Specialty Pharmacy Hospital or Institution Other

Address Line 1: _____

Address Line 2: _____

City: _____ State: _____ Zip: _____

Primary Phone: _____ Secondary Phone: _____

Fax: _____

SHIP TO INFORMATION

Ship To Address (if the same as above, check here)

Ship To Contact Name: _____

Address Line 1: _____

Address Line 2: _____

City: _____ State: _____ Zip: _____

Primary Phone: _____ Secondary Phone: _____

Fax: _____

ADMINISTRATOR INFORMATION

First Name: _____ MI: _____ Last Name: _____

Preferred Method of Communication: Email Fax

Email: _____

Phone: _____ Fax: _____

(if different from above)

(if different from above)

PHARMACY SERVICE PROVIDER AGREEMENT

By signing below, I acknowledge that:

- I have read and understand the ZYPREXA RELPREVV Patient Care Program Instructions Brochure.
- I will ensure that all appropriate pharmacy staff are trained and have read and understand the ZYPREXA RELPREVV Patient Care Program Instructions Brochure.
- 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 and that can allow for continuous patient monitoring for at least 3 hours post-injection.
- 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.
- I will ensure that pharmacy staff will not dispense ZYPREXA RELPREVV directly to patients.
- I will ensure pharmacy staff report the date of each ZYPREXA RELPREVV dispensing to the ZYPREXA RELPREVV Patient Care Program.
- For each dispense I will ensure prescription verification (includes patient eligibility check and recording the dispense date) is completed on the date of dispense, prior to the convenience kit leaving the pharmacy.
- I understand that the ZYPREXA RELPREVV Patient Care Program Coordinating Center may contact the pharmacy to clarify information provided or to obtain information about the patient.

I may cancel this registration by notifying the ZYPREXA RELPREVV Patient Care Program Coordinating Center by fax at 1-877-772-9391 or by phone at 1-877-772-9390. If I cancel, Lilly will cease to supply ZYPREXA RELPREVV to the facility.

Administrator Signature

Date:

--	--	--	--	--	--	--	--

month day year

* Buy & Bill Pharmacy Service Provider - a licensed healthcare provider that purchases pharmaceuticals through a licensed distributor for its own use in the treatment of a patient and then includes the cost of the pharmaceutical in its billing of patients and third-party payers.

PHONE 1-877-772-9390

FAX 1-877-772-9391

www.zyprexarelprevvprogram.com

Version 4.0 XXSept2014

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HEALTHCARE FACILITY REGISTRATION FORM



To be enrolled in the ZYPREXA RELPREVV Patient Care Program, complete and fax this form to 1-877-772-9391.

Training must be completed before a healthcare facility may be enrolled in the ZYPREXA RELPREVV Patient Care Program.

HEALTHCARE FACILITY INFORMATION

Enrollment Reenrollment

Healthcare Facility Name: _____

Please specify location of Healthcare Facilities: Prescriber Office Clinic/Outpatient Facility Hospital Other

Address: _____

City: _____ State: _____ Zip: _____

Phone: _____ Fax: _____

AUTHORIZED HEALTHCARE FACILITY REPRESENTATIVE INFORMATION

First Name: _____ MI: _____ Last Name: _____

Position/Title: _____

Phone: _____ Fax: _____

Email: _____

Preferred Method of Communication: Email Fax

You may identify Delegate(s) to enter the necessary patient data into the Patient Care Program system.

Delegate First Name: _____ MI: _____ Last Name: _____

Facility Name: _____

Phone: _____ Fax: _____
(if different from above) (if different from above)

Email: _____

Delegate First Name: _____ MI: _____ Last Name: _____

Facility Name: _____

Phone: _____ Fax: _____
(if different from above) (if different from above)

Email: _____

Delegate First Name: _____ MI: _____ Last Name: _____

Facility Name: _____

Phone: _____ Fax: _____
(if different from above) (if different from above)

Email: _____

Delegate First Name: _____ MI: _____ Last Name: _____

Facility Name: _____

Phone: _____ Fax: _____
(if different from above) (if different from above)

Email: _____

Delegate First Name: _____ MI: _____ Last Name: _____

Facility Name: _____

Phone: _____ Fax: _____
(if different from above) (if different from above)

Email: _____

If additional Delegates are required contact the the Patient Care Program Coordinating Center.

PHONE 1-877-772-9390

FAX 1-877-772-9391

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HEALTHCARE FACILITY REGISTRATION FORM

HEALTHCARE FACILITY AGREEMENT

As the authorized representative for this facility, I attest that:

- I have read and understand the ZYPREXA RELPREVV Patient Care Program Instructions Brochure;
- I will ensure that all appropriate staff are trained and have read and understand the ZYPREXA RELPREVV Patient Care Program Instructions Brochure as well as the following Training Materials:
 - ZYPREXA RELPREVV Healthcare Professional Training
 - ZYPREXA RELPREVV Reconstitution and Administration Training
- 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 and that can allow for continuous patient monitoring for at least 3 hours post-injection;
- 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;
- 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;
- I will ensure that the Medication Guide is provided to the patient or the patient's legal guardian prior to each injection;
- I will ensure that the appropriate staff monitors the patient continuously for at least 3 hours;
- I will ensure that required data are submitted within 7 days after each injection to the ZYPREXA RELPREVV Patient Care Program.
- I understand that the ZYPREXA RELPREVV Patient Care Program Coordinating Center may contact the health care setting to clarify information provided or to obtain information about the patient.

I confirm that the information above is correct.

I understand that this information will be used to document healthcare facilities that are eligible to administer ZYPREXA RELPREVV.

I also understand that this information may be shared with government agencies.

I understand that Lilly will regularly evaluate ZYPREXA RELPREVV Patient Care Program compliance to ensure that program objectives are met. Lilly reserves the right to terminate a healthcare facility's enrollment at any time based upon non-compliance or to take other appropriate measures to assure that the ZYPREXA RELPREVV Patient Care Program objectives are met.

I may cancel this healthcare facility registration in the future by notifying Lilly in writing and submitting the notification by fax to 1-877-772-9391 or by calling 1-877-772-9390. If I revoke this facility's registration, the facility will no longer be eligible to administer ZYPREXA RELPREVV to patients.

Authorized Healthcare Facility Representative Signature

Date: - -
month day year

Authorized Healthcare Facility Representative Name (print) _____ Title _____

Please fax completed form to the ZYPREXA RELPREVV Patient Care Program at 1-877-772-9391.

PHONE 1-877-772-9390

FAX 1-877-772-9391

www.zyprexarelprevvprogram.com

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MULTIPLE PATIENT INJECTION FORM

INJECTION
Multiple Patients



IMPORTANT: Before administering the injection, confirm there will be someone to accompany the patient after the 3-hour observation period. If this cannot be confirmed, do not give the injection. Submit this information within 7 days after the patient's injection. If you are aware that the patient's prescriber has changed, please notify the ZYPREXA RELPREVV Patient Care Program Coordinating Center.

Injection Facility Name: _____

Date of Injection month day year
 - -

	Patient Info.	Patient Info.	Patient Info.
Patient No.: (PIN)	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
Patient Name:	First Name _____ MI _____ Last Name _____	First Name _____ MI _____ Last Name _____	First Name _____ MI _____ Last Name _____
Date of Birth:	mon h - day - year ____ - ____ - ____	month - day - year ____ - ____ - ____	month - day - year ____ - ____ - ____
PDSS since last visit? (check one)	<input type="checkbox"/> Yes <input type="checkbox"/> No If Yes, has the prescriber been notified of the PDSS event? <input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No If Yes, has the prescriber been notified of the PDSS event? <input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No If Yes, has the prescriber been notified of the PDSS event? <input type="checkbox"/> Yes <input type="checkbox"/> No
Time of Injection (24-hour clock)	<input type="text"/> : <input type="text"/>	<input type="text"/> : <input type="text"/>	<input type="text"/> : <input type="text"/>
Dose of Injection (check one)	<input type="checkbox"/> 150 mg <input type="checkbox"/> 210 mg <input type="checkbox"/> 300 mg <input type="checkbox"/> 405 mg <input type="checkbox"/> Other dose _____ mg	<input type="checkbox"/> 150 mg <input type="checkbox"/> 210 mg <input type="checkbox"/> 300 mg <input type="checkbox"/> 405 mg <input type="checkbox"/> Other dose _____ mg	<input type="checkbox"/> 150 mg <input type="checkbox"/> 210 mg <input type="checkbox"/> 300 mg <input type="checkbox"/> 405 mg <input type="checkbox"/> Other dose _____ mg
Observed at least 3 hours post-injection? (check one)	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
PDSS during onsite observation? (check one)	<input type="checkbox"/> Yes <input type="checkbox"/> No If Yes, has the prescriber been notified of the PDSS event? <input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No If Yes, has the prescriber been notified of the PDSS event? <input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No If Yes, has the prescriber been notified of the PDSS event? <input type="checkbox"/> Yes <input type="checkbox"/> No
Following the injection, was the patient alert, oriented, and absent of any signs and symptoms of PDSS prior to being released from the healthcare facility? (check one)	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
Following the injection, was the patient accompanied from the facility? (check one)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable, patient did not leave facility (in-patient)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable, patient did not leave facility (in-patient)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable, patient did not leave facility (in-patient)
Signature	Healthcare Facility Staff Member Signature _____ <input type="text"/> - <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> month day year Healthcare Facility Staff Member Name (print)	Healthcare Facility Staff Member Signature _____ <input type="text"/> - <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> month day year Healthcare Facility Staff Member Name (print)	Healthcare Facility Staff Member Signature _____ <input type="text"/> - <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> month day year Healthcare Facility Staff Member Name (print)
Was the patient or legal guardian given a Medication Guide prior to this injection?	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No

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PATIENT REGISTRATION FORM COPY

PATIENT
COPY



Provide this copy of the ZYPREXA RELPREVV Patient Care Program Patient Registration Form to the patient or guardian upon enrollment.

PATIENT INFORMATION

First Name: _____ MI: _____ Last Name: _____

Date: _____

PATIENT AGREEMENT

The maker of ZYPREXA RELPREVV, Eli Lilly and Company and their delegates run the ZYPREXA RELPREVV Patient Care Program.

Your doctor will send your name, date of birth, and other information that directly identifies you to the ZYPREXA RELPREVV Patient Care Program. Ask your doctor if you have questions about the information that will be collected.

The ZYPREXA RELPREVV Patient Care Program will collect and use your information in the following ways:

- Your doctor will provide dose, date and time of each injection, and other medical information to the ZYPREXA RELPREVV Patient Care Program.
- Your information will be stored in the ZYPREXA RELPREVV Patient Care Program computer system.
- The information will be used to help Lilly learn more about the safety of ZYPREXA RELPREVV.
- Information from all patients in the ZYPREXA RELPREVV Patient Care Program will be reviewed and may be combined with information from clinical studies.
- This combined information will not be able to identify you or any other patient. This combined information may be shared with:
 - regulatory agencies,
 - doctors at other institutions,
 - the committee overseeing the ZYPREXA RELPREVV Patient Care Program, and/or
 - publications or as part of scientific discussions.

Also, by signing this form you agree to the following:

- I understand that I must enroll in the ZYPREXA RELPREVV Patient Care Program registry to get ZYPREXA RELPREVV.
- I agree to have my information entered in the ZYPREXA RELPREVV Patient Care Program registry.
- My doctor has explained the risks and benefits of treatment with ZYPREXA RELPREVV.
- I have received a copy of the Medication Guide.
- I understand that I will be observed at the clinic for 3 hours after each injection.
- Someone must go with me to my destination when I leave the clinic.
- I understand that I can not drive or use heavy machinery for the rest of the day on which I get an injection.
- I agree to seek medical care right away if I have 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.
- I agree to contact my doctor if I have a reaction to ZYPREXA RELPREVV.
- I may be asked to complete occasional surveys about my understanding of the risks and benefits of treatment with ZYPREXA RELPREVV.
- I or my caregiver have discussed any questions or concerns about my treatment with ZYPREXA RELPREVV with my doctor.

You may stop participating in the ZYPREXA RELPREVV Patient Care Program at any time by telling your doctor. If you stop participating, you will no longer be able to receive the drug. Your doctor will no longer provide any of your information to the ZYPREXA RELPREVV Patient Care Program except to answer safety questions. The ZYPREXA RELPREVV Patient Care Program will still use information that was collected before you stopped participating. You will be provided a copy of this form

PATIENT REGISTRATION FORM

PATIENT
Page 1 of 2



To be enrolled in the ZYPREXA RELPREVV Patient Care Program, complete and fax this form to 1-877-772-9391.

PATIENT INFORMATION

First Name: _____ MI: _____ Last Name: _____

Date of Birth: _____

Gender: Male Female

Race: White Black or African American Native Hawaiian or Other Pacific Islander
 Asian American Indian or Alaska Native Other

Ethnicity: Hispanic or Latino
 Non-Hispanic/Non-Latino

PRESCRIBER INFORMATION

First Name: _____ MI: _____ Last Name: _____

License Number: _____ State of Issue: _____

Treatment Facility/Practice Name (where you see the patient): _____

Address Line 1: _____

Address Line 2: _____

Will the patient be injected/monitored at your facility/practice?

Yes

No (If No, complete next section)

INJECTING/MONITORING FACILITY INFORMATION

Facility Name (where the patient receives injections or monitoring): _____

Address Line 1: _____

Address Line 2: _____

City: _____ State: _____ Zip: _____

PHONE 1-877-772-9390

FAX 1-877-772-9391

www.zyprexarelprevvprogram.com

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PATIENT REGISTRATION FORM

PATIENT AGREEMENT

The maker of ZYPREXA RELPREVV, Eli Lilly and Company and their delegates run the ZYPREXA RELPREVV Patient Care Program.

Your doctor will send your name, date of birth, and other information that directly identifies you to the ZYPREXA RELPREVV Patient Care Program. Ask your doctor if you have questions about the information that will be collected.

The ZYPREXA RELPREVV Patient Care Program will collect and use your information in the following ways:

- Your doctor will provide dose, date and time of each injection, and other medical information to the ZYPREXA RELPREVV Patient Care Program.
- Your information will be stored in the ZYPREXA RELPREVV Patient Care Program computer system.
- The information will be used to help Lilly learn more about the safety of ZYPREXA RELPREVV.
- Information from all patients in the ZYPREXA RELPREVV Patient Care Program will be reviewed and may be combined with information from clinical studies.
- This combined information will not be able to identify you or any other patient. This combined information may be shared with:
 - regulatory agencies,
 - doctors at other institutions,
 - the committee overseeing the ZYPREXA RELPREVV Patient Care Program, and/or
 - publications or as part of scientific discussions.

Also, by signing this form you agree to the following:

- I understand that I must enroll in the ZYPREXA RELPREVV Patient Care Program registry to get ZYPREXA RELPREVV.
- I agree to have my information entered in the ZYPREXA RELPREVV Patient Care Program registry.
- My doctor has explained the risks and benefits of treatment with ZYPREXA RELPREVV.
- I have received a copy of the Medication Guide.
- I understand that I will be observed at the clinic for 3 hours after each injection.
- Someone must go with me to my destination when I leave the clinic.
- I understand that I can not drive or use heavy machinery for the rest of the day on which I get an injection.
- I agree to seek medical care right away if I have 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.
- I agree to contact my doctor if I have a reaction to ZYPREXA RELPREVV.
- I may be asked to complete occasional surveys about my understanding of the risks and benefits of treatment with ZYPREXA RELPREVV.
- I or my caregiver have discussed any questions or concerns about my treatment with ZYPREXA RELPREVV with my doctor.

You may stop participating in the ZYPREXA RELPREVV Patient Care Program at any time by telling your doctor. If you stop participating, you will no longer be able to receive the drug. Your doctor will no longer provide any of your information to the ZYPREXA RELPREVV Patient Care Program except to answer safety questions. The ZYPREXA RELPREVV Patient Care Program will still use information that was collected before you stopped participating. You will be provided a copy of this form.

Signature

Date:

--	--	--	--	--	--

month day year

Printed Name of Patient

Printed Name of Legal Guardian (if applicable)

Check the box if the patient has not signed due to enrollment decision being made by prescriber who is authorized via a court order.

Date of Court Order Expiration (MMDDYYYY) _____

This patient has been shown to be tolerant of oral olanzapine.

Signature of Prescriber

Date:

--	--	--	--	--	--

month day year

Printed Name of Prescriber

PHONE 1-877-772-9390

FAX 1-877-772-9391

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POST-INJECTION DELIRIUM/SEDATION SYNDROME (PDSS) FORM

zyprexaRelprevv[™]
(olanzapine) For Extended Release
Injectable Suspension

Submit this information within **24 hours** of becoming aware of a suspected PDSS event.

Patient No (PIN)	<input type="text"/>									
Patient Name:	First Name		MI	Last Name						
Date of Birth:	<input type="text"/>	<input type="text"/>	-	<input type="text"/>	<input type="text"/>	-	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
	month			day				year		

Does the patient have a diagnosis of schizophrenia? Yes No

PATIENT/INJECTION INFORMATION

Date of Injection: - -

month day year

Convenience Kit Package

Lot # _____

Time of ZYPREXA RELPREVV Injection: :

24-hour clock

ONSET OF FIRST PDSS SYMPTOM AFTER INJECTION (choose only one)

- | | | |
|--|--|---|
| <input type="checkbox"/> 1 - 15 minutes | <input type="checkbox"/> 46 - 60 minutes | <input type="checkbox"/> 121 - 150 minutes (2 ½ hours) |
| <input type="checkbox"/> 16 - 30 minutes | <input type="checkbox"/> 61 - 90 minutes (1 ½ hours) | <input type="checkbox"/> 151 - 180 minutes (3 hours) |
| <input type="checkbox"/> 31 - 45 minutes | <input type="checkbox"/> 91 - 120 minutes (2 hours) | <input type="checkbox"/> If greater than 3 hours please specify:
_____ Hours |

Dose of Injection: 150 mg 210 mg 300 mg 405 mg Other dose _____ mg

Was the injection given in gluteal muscle? Yes No

Height: (inches) Weight: (lbs.)

PDSS SIGNS AND SYMPTOMS

Please mark the signs and symptoms that the patient experienced (check all that apply).

- | | | | |
|---|---|--|--|
| <input type="checkbox"/> Aggressiveness | <input type="checkbox"/> Coma | <input type="checkbox"/> Hypertension | <input type="checkbox"/> Tachycardia |
| <input type="checkbox"/> Agitation | <input type="checkbox"/> Confusion | <input type="checkbox"/> Hypotension | <input type="checkbox"/> Various extrapyramidal symptoms |
| <input type="checkbox"/> Anxiety | <input type="checkbox"/> Convulsion/Seizure | <input type="checkbox"/> Other cognitive impairment | <input type="checkbox"/> Weakness |
| <input type="checkbox"/> Aspiration | <input type="checkbox"/> Delirium | <input type="checkbox"/> Possible neuroleptic malignant syndrome | <input type="checkbox"/> Other _____ |
| <input type="checkbox"/> Ataxia | <input type="checkbox"/> Disorientation | <input type="checkbox"/> Reduced level of consciousness | <input type="checkbox"/> Other _____ |
| <input type="checkbox"/> Cardiac arrhythmias | <input type="checkbox"/> Dizziness | <input type="checkbox"/> Respiratory depression | <input type="checkbox"/> Other _____ |
| <input type="checkbox"/> Cardiopulmonary arrest | <input type="checkbox"/> Dysarthria | <input type="checkbox"/> Sedation | <input type="checkbox"/> Other _____ |

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POST-INJECTION DELIRIUM/SEDATION SYNDROME (PDSS) FORM

Patient No.: (PIN)

Patient Name: _____
First Name MI Last Name

PDSS start date: - -
month day year

PDSS resolution date: - - OR Ongoing
month day year

If resolved, duration of PDSS: _____ Minutes Hours Days

Are these PDSS symptoms related to ZYPREXA RELPREVV?
 Yes
 No - Please Explain _____

Describe the clinical course _____

Patient Outcome: (choose one) Recovered Fatal Not Recovered
 Unknown Recovering Recovered with sequelae

Once a PDSS event was suspected, was the patient's monitoring initiated in a facility capable of resuscitation? Yes No

Did the patient visit the emergency room as a result of the PDSS? Yes No

Was the patient admitted to the hospital as a result of the PDSS? Yes No

Were olanzapine concentrations collected? Yes No

Did the patient receive any **MEDICATIONS AS TREATMENT** for the PDSS event? Yes - Please record below No

Treatment Medication Name	Dose	Duration of Use (in Days)

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POST-INJECTION DELIRIUM/SEDATION SYNDROME (PDSS) FORM

Patient No.: (PIN)

Patient Name: _____
 First Name MI Last Name

Did the patient receive any **NON-PHARMACEUTICAL TREATMENTS** or **DIAGNOSTIC TESTS** associated with this event? Yes - Please record below No

- | | | | |
|---|------------------------------------|---|--|
| <input type="checkbox"/> Assisted ventilation | <input type="checkbox"/> EEG | <input type="checkbox"/> MRI | <input type="checkbox"/> Urine drug screen |
| <input type="checkbox"/> Brain CT | <input type="checkbox"/> IV fluids | <input type="checkbox"/> Observation/symptomatic management | <input type="checkbox"/> Vital sign monitoring |
| <input type="checkbox"/> ECG | <input type="checkbox"/> Labs | <input type="checkbox"/> Restraints | <input type="checkbox"/> Other _____ |

Please fax test results to 1-877-772-9391.

HISTORY PRIOR TO PDSS EVENT

Does the patient have any relevant comorbidities?

- Yes - Please specify: _____
- No

PRIOR MEDICATIONS

Did the patient take any medications during the 24 hours prior to the injection? Yes - Please record below No

Prior Medication Name	Dose	Duration of Use			
		Number	Choose One		
			<input type="checkbox"/> Days	<input type="checkbox"/> Months	<input type="checkbox"/> Years
			<input type="checkbox"/> Days	<input type="checkbox"/> Months	<input type="checkbox"/> Years
			<input type="checkbox"/> Days	<input type="checkbox"/> Months	<input type="checkbox"/> Years
			<input type="checkbox"/> Days	<input type="checkbox"/> Months	<input type="checkbox"/> Years
			<input type="checkbox"/> Days	<input type="checkbox"/> Months	<input type="checkbox"/> Years

Did the patient use any of the following during the 24 hours prior to the injection? Yes - Please record below No

- | | | | |
|--|---------------------------------------|--|--|
| <input type="checkbox"/> Alcohol | <input type="checkbox"/> Barbiturates | <input type="checkbox"/> Cocaine | <input type="checkbox"/> Opiates |
| <input type="checkbox"/> Amphetamines/Methamphetamines | <input type="checkbox"/> Cannabinoid | <input type="checkbox"/> Hallucinogens | <input type="checkbox"/> Phencyclidine |

Event reported by: _____
 First MI Last

Title/Occupation: _____

If agent of the Prescriber, name of Prescriber: _____

Phone 1-877-772-9390

FAX 1-877-772-9391

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PHARMACY REGISTRATION FORM



To be enrolled in the ZYPREXA RELPREVV Patient Care Program, complete and fax this form to 1-877-772-9391.

Training must be completed before a pharmacy may be enrolled in the ZYPREXA RELPREVV Patient Care Program.

PHARMACY INFORMATION

Enrollment Reenrollment

Pharmacy/Hospital Name: _____

Pharmacy DEA Number: _____

Please specify description of Pharmacy: Community/Retail Specialty Pharmacy Hospital or Institution Other

Address Line 1: _____

Address Line 2: _____

City: _____ State: _____ Zip: _____

Primary Phone: _____ Secondary Phone: _____

Fax: _____

SHIP TO INFORMATION

Ship To Address (if the same as above, check here)

Ship To Contact Name: _____

Address Line 1: _____

Address Line 2: _____

City: _____ State: _____ Zip: _____

Primary Phone: _____ Secondary Phone: _____

Fax: _____

PHARMACIST-IN-CHARGE INFORMATION

First Name: _____ MI: _____ Last Name: _____

Email: _____

Phone: _____ Fax: _____
(if different from above) (if different from above)

PHARMACIST-IN-CHARGE INFORMATION

By signing below, I acknowledge that:

- I have read and understand the ZYPREXA RELPREVV Patient Care Program Instructions Brochure.
- I will ensure that all appropriate pharmacy staff are trained and have read and understand the ZYPREXA RELPREVV Patient Care Program Instructions Brochure.
- 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 and that can allow for continuous patient monitoring for at least 3 hours post-injection.
- 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.
- I will ensure that pharmacy staff will not dispense ZYPREXA RELPREVV directly to patients.
- I will ensure pharmacy staff report the date of each ZYPREXA RELPREVV dispensing to the ZYPREXA RELPREVV Patient Care Program.
- For each dispense I will ensure prescription verification (includes patient eligibility check and recording the dispense date) is completed on the date of dispense, prior to the convenience kit leaving the pharmacy.
- 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.

I may cancel this registration by notifying the ZYPREXA RELPREVV Patient Care Program Coordinating Center by fax at 1-877-772-9391 or by phone at 1-877-772-9390. If I cancel, Lilly will cease to supply ZYPREXA RELPREVV to the pharmacy.

Pharmacist-in-Charge Signature Date:

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month day year

PHONE 1-877-772-9390

FAX 1-877-772-9391

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PRESCRIBER REGISTRATION FORM



To be enrolled in the ZYPREXA RELPREVV Patient Care Program, complete and fax this form to 1-877-772-9391.

Training must be completed before a prescriber may be enrolled in the ZYPREXA RELPREVV Patient Care Program.

PRESCRIBER INFORMATION

Enrollment

Reenrollment

First Name: _____ MI: _____ Last Name: _____

Degree: MD DO NP PA Nurse with prescriptive authority Other with prescriptive authority

License Number: _____ State of Issue: _____

Treatment Facility/Practice (Where you see your patients): _____

If you see your patients at multiple locations please contact the ZYPREXA RELPREVV Patient Care Program Coordinating Center to provide additional facility/practice information

Address Line 1: _____

Address Line 2: _____

City: _____ State: _____ Zip: _____

Phone: _____ Alternate Phone: _____

Fax: _____ Prescriber Email: _____

Preferred Method of Communication: Email Fax

PRESCRIBER AGREEMENT

By signing below, I acknowledge that:

- I understand the ZYPREXA RELPREVV Patient Care Program requirements and the risks associated with ZYPREXA RELPREVV.
- I have completed the mandatory ZYPREXA RELPREVV training.
- 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;
- I understand that ZYPREXA RELPREVV should only be initiated in patients for whom tolerability with oral olanzapine has been established;
- I 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.
- I will enroll all patients in the ZYPREXA RELPREVV Patient Care Program registry prior to prescribing ZYPREXA RELPREVV by completing the Patient Registration Form.
- I will ensure all suspected cases of PDSS are reported to the ZYPREXA RELPREVV Patient Care Program within 24 hours of becoming aware of the event.
- I will review the ZYPREXA RELPREVV Medication Guide with each patient prior to prescribing.
- I understand that the ZYPREXA RELPREVV Patient Care Program Coordinating Center may contact me to resolve discrepancies, to obtain information about a patient, or to conduct occasional surveys.

I may cancel this registration by notifying the ZYPREXA RELPREVV Patient Care Program Coordinating Center by fax at 1-877-772-9391 or by phone at 1-877-772-9390.

If I revoke my registration, I will no longer be eligible to prescribe ZYPREXA RELPREVV.

Lilly may disenroll prescribers that are non-compliant with the program requirements.

Prescriber Signature

Date:

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month day year

PHONE 1-877-772-9390

FAX 1-877-772-9391

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SINGLE PATIENT INJECTION FORM

INJECTION

zyprexaRelprevv[™]
(olanzapine) For Extended Release
Injectable Suspension

IMPORTANT: Before administering the injection, confirm there will be someone to accompany the patient after the 3-hour observation period. If this cannot be confirmed, do not give the injection.

Submit this information within 7 days after the patient's injections. If you are aware that the patient's prescriber has changed, please notify the ZYPREXA RELPREVV Patient Care Program Coordinating Center.

Patient No.: (PIN)	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Injection Facility Name: _____
Patient Name:	First _____ MI _____ Last _____	
Date of Birth:	<input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> month day year	

PDSS since the last visit? (After the patient left the office, following his/her previous injection, did the patient experience post-injection delirium/sedation syndrome?)

No Yes

If Yes, has the prescriber been notified of the PDSS event?

Yes No

ZYPREXA RELPREVV TREATMENT

Date of Injection: - -
month day year

Time of ZYPREXA RELPREVV injection: :
24-hour clock

Dose of Injection: 150 mg 210 mg 300 mg 405 mg Other dose _____ mg

Was the patient observed for at least 3 hours post-injection? Yes No

Did the patient experience post-injection delirium/sedation syndrome during the onsite post-injection observational period?

No Yes

If Yes, has the prescriber been notified of the PDSS event? Yes No

Following the injection, was the patient alert, oriented, and absent of any signs and symptoms of PDSS prior to being released from the healthcare facility?

Yes No

Following the injection, was the patient accompanied from the facility?

Yes No Not applicable, patient did not leave facility (in-patient)

Was the patient or legal guardian given a Medication Guide prior to this injection? Yes No

Healthcare Facility Staff Member Signature _____ DATE: - -
month day year

Healthcare Facility Staff Member Name (print): _____

PHONE 1-877-772-9390

FAX 1-877-772-9391

www.zyprexarelprevvprogram.com

Version 2.0 03Aug2012

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZYPREXA RELPREVV safely and effectively. See full prescribing information for ZYPREXA RELPREVV.

ZYPREXA RELPREVV (olanzapine) For Extended Release Injectable Suspension

Initial U.S. Approval: 1996

WARNING: POST-INJECTION DELIRIUM/SEDATION SYNDROME AND INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

- Patients are at risk for severe sedation (including coma) and/or delirium after each injection and must be observed for at least 3 hours in a registered facility with ready access to emergency response services. Because of this risk, ZYPREXA RELPREVV is available only through a restricted distribution program called ZYPREXA RELPREVV Patient Care Program and requires prescriber, healthcare facility, patient, and pharmacy enrollment. (2.1, 5.1, 5.2, 10.2, 17.2)
- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ZYPREXA RELPREVV is not approved for the treatment of patients with dementia-related psychosis. (5.3, 5.16, 17.3)

RECENT MAJOR CHANGES

None.

INDICATIONS AND USAGE

ZYPREXA® RELPREVV™ is a long-acting atypical antipsychotic for intramuscular injection indicated for the treatment of schizophrenia. (1.1)

Efficacy was established in two clinical trials in patients with schizophrenia: one 8-week trial in adults and one maintenance trial in adults. (14.1)

DOSAGE AND ADMINISTRATION

150 mg/2 wks, 300 mg/4 wks, 210 mg/2 wks, 405 mg/4 wks, or 300 mg/2 wks. See Table 1 for dosing recommendations. (2.1)

ZYPREXA RELPREVV is intended for deep intramuscular gluteal injection only.

- Do not administer intravenously or subcutaneously. (2.1)
- Be aware that there are two ZYPREXA intramuscular formulations with different dosing schedules. ZYPREXA IntraMuscular (10 mg/vial) is a short-acting formulation and should not be confused with ZYPREXA RELPREVV. (2.1)
- Establish tolerability with oral olanzapine prior to initiating treatment. (2.1)
- ZYPREXA RELPREVV doses above 405 mg every 4 weeks or 300 mg every 2 weeks have not been evaluated in clinical trials. (2.1)
- Use in specific populations (including renal and hepatic impaired, and pediatric population) has not been studied. (2.1)
- Must be suspended using only the diluent for ZYPREXA RELPREVV provided in the convenience kit. (2.2)

DOSAGE FORMS AND STRENGTHS

Powder for suspension for intramuscular use only: 210 mg/vial, 300 mg/vial, and 405 mg/vial (3, 11, 16)

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

- **Elderly Patients with Dementia-Related Psychosis:** Increased risk of death and increased incidence of cerebrovascular adverse events (e.g. stroke, transient ischemic attack). (5.3)
- **Suicide:** The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high-risk patients should accompany drug therapy. (5.4)

- **Neuroleptic Malignant Syndrome:** Manage with immediate discontinuation and close monitoring. (5.5)
- **Hyperglycemia:** In some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients taking olanzapine. Patients taking olanzapine should be monitored for symptoms of hyperglycemia and undergo fasting blood glucose testing at the beginning of, and periodically during, treatment. (5.6)
- **Hyperlipidemia:** Undesirable alterations in lipids have been observed. Appropriate clinical monitoring is recommended, including fasting blood lipid testing at the beginning of, and periodically during, treatment. (5.7)
- **Weight Gain:** Potential consequences of weight gain should be considered. Patients should receive regular monitoring of weight. (5.8)
- **Tardive Dyskinesia:** Discontinue if clinically appropriate. (5.9)
- **Orthostatic Hypotension:** Orthostatic hypotension associated with dizziness, tachycardia, bradycardia and, in some patients, syncope, may occur especially during initial dose titration. Use caution in patients with cardiovascular disease, cerebrovascular disease, and those conditions that could affect hemodynamic responses. (5.10)
- **Leukopenia, Neutropenia, and Agranulocytosis:** Has been reported with antipsychotics, including ZYPREXA. Patients with a history of a clinically significant low white blood cell count (WBC) or drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of ZYPREXA RELPREVV should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors. (5.11)
- **Seizures:** Use cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold. (5.13)
- **Potential for Cognitive and Motor Impairment:** Has potential to impair judgment, thinking, and motor skills. Use caution when operating machinery. (5.14)
- **Hyperprolactinemia:** May elevate prolactin levels. (5.17)
- **Laboratory Tests:** Monitor fasting blood glucose and lipid profiles at the beginning of, and periodically during, treatment. (5.18)

ADVERSE REACTIONS

Most common adverse reactions (≥5% in at least one of the treatment groups and greater than placebo) associated with ZYPREXA RELPREVV treatment: headache, sedation, weight gain, cough, diarrhea, back pain, nausea, somnolence, dry mouth, nasopharyngitis, increased appetite, and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- **CNS Acting Drugs:** Caution should be used when used in combination with other centrally acting drugs and alcohol. (7.2)
- **Antihypertensive Agents:** Enhanced antihypertensive effect. (7.2)
- **Levodopa and Dopamine Agonists:** May antagonize levodopa/dopamine agonists. (7.2)
- **Diazepam:** May potentiate orthostatic hypotension. (7.1, 7.2)
- **Alcohol:** May potentiate orthostatic hypotension. (7.1)
- **Carbamazepine:** Increased clearance of olanzapine. (7.1)
- **Fluvoxamine:** May increase olanzapine levels. (7.1)

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** ZYPREXA RELPREVV should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)
- **Nursing Mothers:** Breast-feeding is not recommended. (8.3)
- **Pediatric Use:** Safety and effectiveness of ZYPREXA RELPREVV in children <18 years of age have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide

Revised: 07/2011

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FULL PRESCRIBING INFORMATION

WARNING: POST-INJECTION DELIRIUM/SEDATION SYNDROME AND INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Post-Injection Delirium/Sedation Syndrome — Adverse events with signs and symptoms consistent with olanzapine overdose, in particular, sedation (including coma) and/or delirium, have been reported following injections of ZYPREXA RELPREVV. ZYPREXA RELPREVV must be administered in a registered healthcare facility with ready access to emergency response services. After each injection, patients must be observed at the healthcare facility by a healthcare professional for at least 3 hours. Because of this risk, ZYPREXA RELPREVV is available only through a restricted distribution program called ZYPREXA RELPREVV Patient Care Program and requires prescriber, healthcare facility, patient, and pharmacy enrollment [see *Dosage and Administration (2.1)*, *Warnings and Precautions (5.1, 5.2)*, *Overdosage (10.2)*, and *Patient Counseling Information (17.2)*].

Increased Mortality in Elderly Patients with Dementia-Related Psychosis — Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. ZYPREXA RELPREVV is not approved for the treatment of patients with dementia-related psychosis [see *Warnings and Precautions (5.3, 5.16)* and *Patient Counseling Information (17.3)*].

1 INDICATIONS AND USAGE

ZYPREXA RELPREVV is available only through a restricted distribution program [see *Warnings and Precautions (5.2)*]. ZYPREXA RELPREVV must not be dispensed directly to a patient. For a patient to receive treatment, the prescriber, healthcare facility, patient, and pharmacy must all be enrolled in the ZYPREXA RELPREVV Patient Care Program. To enroll, call 1-877-772-9390.

1.1 Schizophrenia

ZYPREXA RELPREVV is indicated for the treatment of schizophrenia. Efficacy was established in two clinical trials in patients with schizophrenia: one 8-week trial in adults and one maintenance trial in adults [see *Clinical Studies (14.1)*].

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

ZYPREXA RELPREVV is intended for deep intramuscular gluteal injection only and should not be administered intravenously or subcutaneously.

Be aware that there are two ZYPREXA intramuscular formulations with different dosing schedules. ZYPREXA IntraMuscular (10 mg/vial) is a short-acting formulation and should not be confused with ZYPREXA RELPREVV. Refer to the package insert for ZYPREXA IntraMuscular for more information about that product.

Establish tolerability with oral olanzapine prior to initiating treatment.

ZYPREXA RELPREVV should be administered by a healthcare professional every 2 to 4 weeks by deep intramuscular gluteal injection using a 19-gauge, 1.5-inch needle. Following insertion of the needle into the muscle, aspiration should be maintained for several seconds to ensure that no blood is drawn into the syringe. If any blood is aspirated into the syringe, it should be discarded and fresh drug should be prepared using a new convenience kit. The injection should be performed at a steady, continuous pressure. Do not massage the injection site.

Dose Selection — The efficacy of ZYPREXA RELPREVV has been demonstrated within the range of 150 mg to 300 mg administered every 2 weeks and with 405 mg administered every 4 weeks. Dose recommendations considering oral ZYPREXA and ZYPREXA RELPREVV are shown in Table 1.

Table 1: Recommended Dosing for ZYPREXA RELPREVV Based on Correspondence to Oral ZYPREXA Doses

Target Oral ZYPREXA Dose	Dosing of ZYPREXA RELPREVV During the First 8 Weeks	Maintenance Dose After 8 Weeks of ZYPREXA RELPREVV Treatment
10 mg/day	210 mg/2 weeks or 405 mg/4 weeks	150 mg/2 weeks or 300 mg/4 weeks
15 mg/day	300 mg/2 weeks	210 mg/2 weeks or 405 mg/4 weeks
20 mg/day	300 mg/2 weeks	300 mg/2 weeks

ZYPREXA RELPREVV doses greater than 405 mg every 4 weeks or 300 mg every 2 weeks have not been evaluated in clinical trials.

Post-Injection Delirium/Sedation Syndrome — During premarketing clinical studies, adverse events that presented with signs and symptoms consistent with olanzapine overdose, in particular, sedation (including coma) and/or delirium, were reported in patients following an injection of ZYPREXA RELPREVV [see *Boxed Warning, Warnings and Precautions (5.1)*, and *Overdosage (10.1)*]. Patients should be informed of this risk and how to recognize related symptoms [see *Patient Counseling Information (17.1, 17.2)*]. ZYPREXA RELPREVV must be administered in a registered healthcare facility with ready access to emergency response services. After each ZYPREXA RELPREVV injection, a healthcare professional must continuously observe the patient at the healthcare facility for at least 3 hours for symptoms consistent with olanzapine overdose, including sedation (ranging from mild to severity to coma) and/or delirium (including confusion, disorientation, agitation, anxiety, and other cognitive impairment). Other symptoms noted include extrapyramidal symptoms, dysarthria, ataxia, aggression, dizziness, weakness, hypertension, and convulsion. The potential for onset of an event is greatest within the first hour. The majority of cases have occurred within the first 3 hours after injection; however, the event has occurred after 3 hours. Following the 3-hour observation period, healthcare professionals must confirm that the patient is alert, oriented, and absent of any signs and symptoms of post-injection delirium/sedation syndrome prior to being released. All patients must be accompanied to their destination upon leaving the facility. For the remainder of the day of each injection, patients should not drive or operate heavy machinery, and should be advised to be vigilant for symptoms of post-injection delirium/sedation syndrome and be able to obtain medical assistance if needed.

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If post-injection delirium/sedation syndrome is suspected, close medical supervision and monitoring should be instituted in a facility capable of resuscitation [see *Overdosage (10)*].

Dosing in Specific Populations — Tolerance of oral ZYPREXA should be established prior to initiating treatment with ZYPREXA RELPREVV. The recommended starting dose is ZYPREXA RELPREVV 150 mg/4 wks in patients who are debilitated, who have a predisposition to hypotensive reactions, who otherwise exhibit a combination of factors that may result in slower metabolism of olanzapine (e.g., nonsmoking female patients ≥65 years of age), or who may be more pharmacodynamically sensitive to olanzapine. When indicated, dose escalation should be undertaken with caution in these patients [see *Warnings and Precautions (5.4)*, *Drug Interactions (7)*, and *Clinical Pharmacology (12.3)*].

ZYPREXA RELPREVV has not been studied in subjects under 18 years of age [see *Warnings and Precautions (5.6, 5.7, and 5.8)*].

Maintenance Treatment — Although no controlled studies have been conducted to determine how long patients should be treated with ZYPREXA RELPREVV, efficacy has been demonstrated over a period of 24 weeks in patients with stabilized schizophrenia. Additionally, oral ZYPREXA has been shown to be effective in maintenance of treatment response in schizophrenia in longer-term use. Patients should be periodically reassessed to determine the need for continued treatment.

Switching from Other Antipsychotics — There are no systematically collected data to specifically address how to switch patients with schizophrenia from other antipsychotics to ZYPREXA RELPREVV.

2.2 Instructions to Reconstitute and Administer ZYPREXA RELPREVV

For deep intramuscular gluteal injection only. Not to be injected intravenously or subcutaneously.

Step 1: Preparing Materials

Convenience kit includes:

- Vial of ZYPREXA RELPREVV powder
- 3-mL vial of diluent
- One 3-mL syringe with pre-attached 19-gauge, 1.5-inch (38 mm) Hypodermic Needle-Pro® needle with needle protection device
- Two 19-gauge, 1.5-inch (38 mm) Hypodermic Needle-Pro needles with needle protection device — For obese patients, a 2-inch (50 mm), 19-gauge or larger needle (not included in convenience kit) may be used for administration.

ZYPREXA RELPREVV must be suspended using only the diluent supplied in the convenience kit.

It is recommended that gloves are used when reconstituting, as ZYPREXA RELPREVV may be irritating to the skin. Flush with water if contact is made with skin.

See additional insert entitled "Instructions to Reconstitute and Administer ZYPREXA RELPREVV" (included) for more information regarding the safe and effective use of the Hypodermic Needle-Pro syringe and needle.

Step 2: Determining Reconstitution Volume

Refer to the table below to determine the amount of diluent to be added to powder for reconstitution of each vial strength.

It is important to note that there is more diluent in the vial than is needed to reconstitute.

Dose	Vial Strength	Diluent to Add
150 mg	210 mg	1.3 mL
210 mg	210 mg	1.3 mL
300 mg	300 mg	1.8 mL
405 mg	405 mg	2.3 mL

Step 3: Reconstituting ZYPREXA RELPREVV

Please read the Hypodermic Needle-Pro Instructions for Use before proceeding with Step 3. Failure to follow these instructions may result in a needlestick injury.

Loosen the powder by lightly tapping the vial.

Open the prepackaged Hypodermic Needle-Pro syringe and needle with needle protection device.

Withdraw the pre-determined diluent volume (Step 2) into the syringe.

Inject the diluent into the powder vial.

Withdraw air to equalize the pressure in the vial by pulling back slightly on the plunger in the syringe.

Remove the needle from the vial, holding the vial upright to prevent any loss of material.

Engage the needle safety device (refer to complete Hypodermic Needle-Pro Instructions for Use).

Pad a hard surface to cushion impact (see Figure 1). Tap the vial firmly and repeatedly on the surface until no powder is visible.

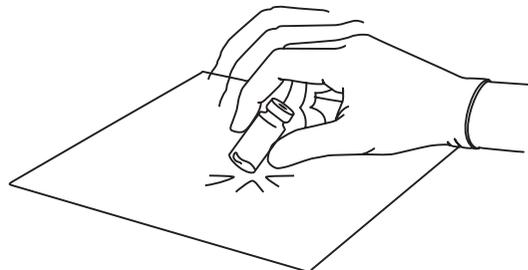


Figure 1: Tap firmly to mix.

Visually check the vial for clumps. Unsuspended powder appears as yellow, dry clumps clinging to the vial. Additional tapping may be required if large clumps remain (see Figure 2).

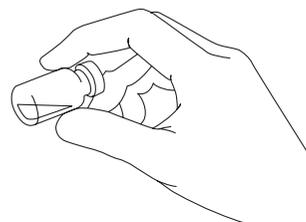


Figure 2: Check for unsuspended powder and repeat tapping if needed.

Shake the vial vigorously until the suspension appears smooth and is consistent in color and texture. The suspended product will be yellow and opaque (see Figure 3).

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Figure 3: Vigorously shake vial.

If foam forms, let vial stand to allow foam to dissipate.

If the product is not used right away, it should be shaken vigorously to re-suspend. Reconstituted ZYPREXA RELPREV remains stable for up to 24 hours in the vial.

Step 4: Injecting ZYPREXA RELPREV

Before administering the injection, confirm there will be someone to accompany the patient after the 3-hour observation period. If this cannot be confirmed, do not give the injection.

Refer to the table below to determine the final volume to inject. Suspension concentration is 150mg/mL ZYPREXA RELPREV.

Dose	Final Volume to Inject
150 mg	1 mL
210 mg	1.4 mL
300 mg	2 mL
405 mg	2.7 mL

Attach a new safety needle to the syringe.

Slowly withdraw the desired amount into the syringe.

Some excess product will remain in the vial.

Engage the needle safety device and remove needle from syringe.

For administration, select the 19-gauge, 1.5-inch (38 mm) Hypodermic Needle-Pro needle with needle protection device. For obese patients, a 2-inch (50 mm), 19-gauge or larger needle (not included in convenience kit) may be used. To help prevent clogging, a 19-gauge or larger needle must be used.

Attach the new safety needle to the syringe prior to injection. Once the suspension has been removed from the vial, it should be injected immediately.

For deep intramuscular gluteal injection only. Do not inject intravenously or subcutaneously. Select and prepare a site for injection in the gluteal area.

After insertion of the needle into the muscle, aspirate for several seconds to ensure that no blood appears. If any blood is drawn into the syringe, discard the syringe and the dose and begin with a new convenience kit. The injection should be performed with steady, continuous pressure.

Do not massage the injection site.

Engage the needle safety device.

Dispose of the vials, needles, and syringe appropriately after injection. The vial is for single-use only.

3 DOSAGE FORMS AND STRENGTHS

ZYPREXA RELPREV is a powder for suspension for intramuscular use only. ZYPREXA RELPREV is present as a yellow solid in a glass vial equivalent to 210, 300, or 405 mg olanzapine per vial. The diluent is a clear, colorless to slightly yellow solution in a glass vial [see Description (11) and How Supplied/Storage and Handling (16)]. The reconstituted suspension will be yellow and opaque [see Dosage and Administration (2.2)].

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Post-Injection Delirium/Sedation Syndrome

During premarketing clinical studies of ZYPREXA RELPREV, adverse events that presented with signs and symptoms consistent with olanzapine overdose, in particular, sedation (including coma) and/or delirium, were reported in patients following an injection of ZYPREXA RELPREV [see Boxed Warning and Dosage and Administration (2.1)]. These events occurred in <0.1% of injections and in approximately 2% of patients who received injections for up to 46 months. These events were correlated with an unintentional rapid increase in serum olanzapine concentrations to supra-therapeutic ranges in some cases. While a rapid and greater than expected increase in serum olanzapine concentration has been observed in some patients with these events, the exact mechanism by which the drug was unintentionally introduced into the blood stream is not known. Clinical signs and symptoms included dizziness, confusion, disorientation, slurred speech, altered gait, difficulty ambulating, weakness, agitation, extrapyramidal symptoms, hypertension, convulsion, and reduced level of consciousness ranging from mild sedation to coma. Time after injection to event ranged from soon after injection to greater than 3 hours after injection. The majority of patients were hospitalized and some required supportive care, including intubation, in several cases. All patients had largely recovered by 72 hours. The risk of an event is the same at each injection, so the risk per patient is cumulative (i.e., increases with the number of injections) [see Overdosage (10.1)].

Healthcare professionals are advised to discuss this potential risk with patients each time they prescribe and administer ZYPREXA RELPREV [see Patient Counseling Information (17.1, 17.2)].

5.2 Prescribing and Distribution Program for ZYPREXA RELPREV

ZYPREXA RELPREV is available only through a restricted distribution program [see Boxed Warning, Indications and Usage (1), and Patient Counseling Information (17.2)]. ZYPREXA RELPREV must not be dispensed directly to a patient. For a patient to receive treatment, the prescriber, healthcare facility, patient, and pharmacy must all be enrolled in the ZYPREXA RELPREV Patient Care Program. To enroll, call 1-877-772-9390.

ZYPREXA RELPREV must be administered in a registered healthcare facility (such as a hospital, clinic, residential treatment center, or community healthcare center) with ready access to emergency response services. After each ZYPREXA RELPREV injection, a healthcare professional must continuously observe the patient at the healthcare facility for at least 3 hours and must confirm that the patient is alert, oriented, and absent of any signs and symptoms of post-injection delirium/sedation syndrome prior to being released. All patients must be accompanied to their destination upon leaving the facility. For the remainder of the day of each injection, patients should not drive or operate heavy machinery, and should be advised to be vigilant for symptoms of post-injection delirium/sedation syndrome and be able to obtain medical assistance if needed. If post-injection delirium/sedation syndrome is suspected, close medical supervision and monitoring should be instituted in a facility capable of resuscitation [see Overdosage (10)]. If parenteral benzodiazepines are required for patient management during an event of post-injection delirium/sedation syndrome, careful evaluation of clinical status for excessive sedation and cardiorespiratory depression is recommended.

5.3 Elderly Patients with Dementia-Related Psychosis Increased Mortality

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ZYPREXA RELPREV is not approved for the treatment of patients with dementia-

related psychosis [see Boxed Warning, Warnings and Precautions (5.16), and Patient Counseling Information (17.3)].

In placebo-controlled oral olanzapine clinical trials of elderly patients with dementia-related psychosis, the incidence of death in olanzapine-treated patients was significantly greater than placebo-treated patients (3.5% vs 1.5%, respectively).

Cerebrovascular Adverse Events (CVAE), Including Stroke

Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients in trials of oral olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with oral olanzapine compared to patients treated with placebo. ZYPREXA RELPREV is not approved for the treatment of patients with dementia-related psychosis [see Boxed Warning and Patient Counseling Information (17.3)].

5.4 Suicide

The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high-risk patients should accompany drug therapy.

5.5 Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including olanzapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered and tolerability with oral olanzapine should be established prior to initiating treatment with ZYPREXA RELPREV [see Dosage and Administration (2.1)]. The patient should be carefully monitored, since recurrences of NMS have been reported [see Patient Counseling Information (17.4)].

5.6 Hyperglycemia

Physicians should consider the risks and benefits when prescribing olanzapine to patients with an established diagnosis of diabetes mellitus, or having borderline increased blood glucose level (fasting 100-126 mg/dL, nonfasting 140-200 mg/dL). Patients taking olanzapine should be monitored regularly for worsening of glucose control. Patients starting treatment with olanzapine should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug [see Patient Counseling Information (17.5)].

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including olanzapine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics. While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics.

Mean increases in blood glucose have been observed in patients treated (median exposure of 9.2 months) with olanzapine in phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). The mean increase of serum glucose (fasting and nonfasting samples) from baseline to the average of the 2 highest serum concentrations was 15.0 mg/dL.

In a study of healthy volunteers, subjects who received olanzapine (N=22) for 3 weeks had a mean increase compared to baseline in fasting blood glucose of 2.3 mg/dL. Placebo-treated subjects (N=19) had a mean increase in fasting blood glucose compared to baseline of 0.34 mg/dL.

Olanzapine Monotherapy in Adults—In an analysis of 5 placebo-controlled adult olanzapine monotherapy studies with a median treatment duration of approximately 3 weeks, olanzapine was associated with a greater mean change in fasting glucose levels compared to placebo (2.76 mg/dL versus 0.17 mg/dL). The difference in mean changes between olanzapine and placebo was greater in patients with evidence of glucose dysregulation at baseline (patients diagnosed with diabetes mellitus or related adverse reactions, patients treated with anti-diabetic agents, patients with a baseline random glucose level ≥ 200 mg/dL, and/or a baseline fasting glucose level ≥ 126 mg/dL).

Olanzapine-treated patients had a greater mean HbA_{1c} increase from baseline of 0.04% (median exposure 21 days), compared to a mean HbA_{1c} decrease of 0.06% in placebo-treated subjects (median exposure 17 days).

In an analysis of 8 placebo-controlled studies (median treatment exposure 4-5 weeks), 6.1% of olanzapine-treated subjects (N=855) had treatment-emergent glycosuria compared to 2.8% of placebo-treated subjects (N=599). Table 2 shows short-term and long-term changes in fasting glucose levels from adult olanzapine monotherapy studies.

Table 2: Changes in Fasting Glucose Levels from Adult Olanzapine Monotherapy Studies

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	Up to 12 weeks exposure		At least 48 weeks exposure	
			N	Patients	N	Patients
Fasting Glucose	Normal to High (<100 mg/dL to ≥ 126 mg/dL)	Olanzapine	543	2.2%	345	12.8%
		Placebo	293	3.4%	NA*	NA*
	Borderline to High (≥ 100 mg/dL and <126 mg/dL to ≥ 126 mg/dL)	Olanzapine	178	17.4%	127	26.0%
		Placebo	96	11.5%	NA*	NA*

* Not Applicable.

The mean change in fasting glucose for patients exposed at least 48 weeks was 4.2 mg/dL (N=487). In analyses of patients who completed 9-12 months of olanzapine therapy, mean change in fasting and nonfasting glucose levels continued to increase over time.

Olanzapine Monotherapy in Adolescents — The safety and efficacy of ZYPREXA RELPREV have not been established in patients under the age of 18 years.

In an analysis of 3 placebo-controlled oral olanzapine monotherapy studies of adolescent patients (13-17 years), including those with schizophrenia (6 weeks) or bipolar I disorder (manic or mixed episodes) (3 weeks), olanzapine was associated with a greater mean change from baseline in fasting glucose levels compared to placebo (2.68 mg/dL versus -2.59 mg/dL). The mean change in fasting glucose for adolescents exposed at least 24 weeks was 3.1 mg/dL (N=121). Table 3 shows short-term and long-term changes in fasting blood glucose from adolescent oral olanzapine monotherapy studies.

Table 3: Changes in Fasting Glucose Levels from Adolescent Oral Olanzapine Monotherapy Studies

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	Up to 12 weeks exposure		At least 24 weeks exposure	
			N	Patients	N	Patients
Fasting Glucose	Normal to High (<100 mg/dL to ≥126 mg/dL)	Olanzapine	124	0%	108	0.9%
		Placebo	53	1.9%	NA ^a	NA ^a
	Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL)	Olanzapine	14	14.3%	13	23.1%
		Placebo	13	0%	NA ^a	NA ^a

^a Not Applicable.

5.7 Hyperlipidemia

Undesirable alterations in lipids have been observed with olanzapine use. Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using olanzapine, is recommended [see Patient Counseling Information (17.6)].

Clinically significant, and sometimes very high (>500 mg/dL), elevations in triglyceride levels have been observed with olanzapine use. Modest mean increases in total cholesterol have also been seen with olanzapine use.

Olanzapine Monotherapy in Adults — In an analysis of 5 placebo-controlled olanzapine monotherapy studies with treatment duration up to 12 weeks, olanzapine-treated patients had increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.3 mg/dL, 3.0 mg/dL, and 20.8 mg/dL respectively compared to decreases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 6.1 mg/dL, 4.3 mg/dL, and 10.7 mg/dL for placebo-treated patients. For fasting HDL cholesterol, no clinically meaningful differences were observed between olanzapine-treated patients and placebo-treated patients. Mean increases in fasting lipid values (total cholesterol, LDL cholesterol, and triglycerides) were greater in patients without evidence of lipid dysregulation at baseline, where lipid dysregulation was defined as patients diagnosed with dyslipidemia or related adverse reactions, patients treated with lipid lowering agents, or patients with high baseline lipid levels.

In long-term studies (at least 48 weeks), patients had increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.6 mg/dL, 2.5 mg/dL, and 18.7 mg/dL, respectively, and a mean decrease in fasting HDL cholesterol of 0.16 mg/dL. In an analysis of patients who completed 12 months of therapy, the mean nonfasting total cholesterol did not increase further after approximately 4-6 months.

The proportion of patients who had changes (at least once) in total cholesterol, LDL cholesterol or triglycerides from normal or borderline to high, or changes in HDL cholesterol from normal or borderline to low, was greater in long-term studies (at least 48 weeks) as compared with short-term studies. Table 4 shows categorical changes in fasting lipids values.

Table 4: Changes in Fasting Lipids Values from Adult Olanzapine Monotherapy Studies

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	Up to 12 weeks exposure		At least 48 weeks exposure	
			N	Patients	N	Patients
Fasting Triglycerides	Increase by ≥50 mg/dL	Olanzapine	745	39.6%	487	61.4%
		Placebo	402	26.1%	NA ^a	NA ^a
	Normal to High (<150 mg/dL to ≥200 mg/dL)	Olanzapine	457	9.2%	293	32.4%
		Placebo	251	4.4%	NA ^a	NA ^a
Borderline to High (≥150 mg/dL and <200 mg/dL to ≥200 mg/dL)	Olanzapine	135	39.3%	75	70.7%	
	Placebo	65	20.0%	NA ^a	NA ^a	
Fasting Total Cholesterol	Increase by ≥40 mg/dL	Olanzapine	745	21.6%	489	32.9%
		Placebo	402	9.5%	NA ^a	NA ^a
	Normal to High (<200 mg/dL to ≥240 mg/dL)	Olanzapine	392	2.8%	283	14.8%
		Placebo	207	2.4%	NA ^a	NA ^a
Borderline to High (≥200 mg/dL and <240 mg/dL to ≥240 mg/dL)	Olanzapine	222	23.0%	125	55.2%	
	Placebo	112	12.5%	NA ^a	NA ^a	
Fasting LDL Cholesterol	Increase by ≥30 mg/dL	Olanzapine	536	23.7%	483	39.8%
		Placebo	304	14.1%	NA ^a	NA ^a
	Normal to High (<100 mg/dL to ≥160 mg/dL)	Olanzapine	154	0%	123	7.3%
		Placebo	82	1.2%	NA ^a	NA ^a
Borderline to High (≥100 mg/dL and <160 mg/dL to ≥160 mg/dL)	Olanzapine	302	10.6%	284	31.0%	
	Placebo	173	8.1%	NA ^a	NA ^a	

^a Not Applicable.

In phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), over a median exposure of 9.2 months, the mean increase in triglycerides in patients taking olanzapine was 40.5 mg/dL. In phase 1 of CATIE, the mean increase in total cholesterol was 9.4 mg/dL.

Olanzapine Monotherapy in Adolescents — The safety and efficacy of ZYPREXA RELPREV have not been established in patients under the age of 18 years.

In an analysis of 3 placebo-controlled oral olanzapine monotherapy studies of adolescents (13-17 years), including those with schizophrenia (6 weeks) or bipolar I disorder (manic or mixed episodes) (3 weeks), olanzapine-treated adolescents had increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 12.9 mg/dL, 6.5 mg/dL, and 28.4 mg/dL, respectively, compared to increases from baseline in mean fasting total cholesterol and LDL cholesterol of 1.3 mg/dL and 1.0 mg/dL, and a decrease in triglycerides of 1.1 mg/dL for placebo-treated adolescents. For fasting HDL cholesterol, no clinically meaningful differences were observed between olanzapine-treated adolescents and placebo-treated adolescents.

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In long-term studies (at least 24 weeks), adolescents had increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.5 mg/dL, 5.4 mg/dL, and 20.5 mg/dL, respectively, and a mean decrease in fasting HDL cholesterol of 4.5 mg/dL. Table 5 shows categorical changes in fasting lipids values in adolescents.

Table 5: Changes in Fasting Lipids Values from Adolescent Oral Olanzapine Monotherapy Studies

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	Up to 6 weeks exposure		At least 24 weeks exposure	
			N	Patients	N	Patients
Fasting Triglycerides	Increase by ≥50 mg/dL	Olanzapine	138	37.0%	122	45.9%
		Placebo	66	15.2%	NA ^a	NA ^a
	Normal to High (<90 mg/dL to ≥130 mg/dL)	Olanzapine	67	26.9%	66	36.4%
		Placebo	28	10.7%	NA ^a	NA ^a
Borderline to High (≥90 mg/dL and <130 mg/dL to ≥130 mg/dL)	Olanzapine	37	59.5%	31	64.5%	
	Placebo	17	35.3%	NA ^a	NA ^a	
Fasting Total Cholesterol	Increase by ≥40 mg/dL	Olanzapine	138	14.5%	122	14.8%
		Placebo	66	4.5%	NA ^a	NA ^a
	Normal to High (<170 mg/dL to ≥200 mg/dL)	Olanzapine	87	6.9%	78	7.7%
		Placebo	43	2.3%	NA ^a	NA ^a
Borderline to High (≥170 mg/dL and <200 mg/dL to ≥200 mg/dL)	Olanzapine	36	38.9%	33	57.6%	
	Placebo	13	7.7%	NA ^a	NA ^a	
Fasting LDL Cholesterol	Increase by ≥30 mg/dL	Olanzapine	137	17.5%	121	22.3%
		Placebo	63	11.1%	NA ^a	NA ^a
	Normal to High (<110 mg/dL to ≥130 mg/dL)	Olanzapine	98	5.1%	92	10.9%
		Placebo	44	4.5%	NA ^a	NA ^a
Borderline to High (≥110 mg/dL and <130 mg/dL to ≥130 mg/dL)	Olanzapine	29	48.3%	21	47.6%	
	Placebo	9	0%	NA ^a	NA ^a	

^a Not Applicable.

5.8 Weight Gain

Potential consequences of weight gain should be considered prior to starting olanzapine. Patients receiving olanzapine should receive regular monitoring of weight [see Patient Counseling Information (17.7)].

Olanzapine Monotherapy in Adults — In an analysis of 13 placebo-controlled olanzapine monotherapy studies, olanzapine-treated patients gained an average of 2.6 kg (5.7 lb) compared to an average 0.3 kg (0.6 lb) weight loss in placebo-treated patients with a median exposure of 6 weeks; 22.2% of olanzapine-treated patients gained at least 7% of their baseline weight, compared to 3% of placebo-treated patients, with a median exposure to event of 8 weeks; 4.2% of olanzapine-treated patients gained at least 15% of their baseline weight, compared to 0.3% of placebo-treated patients, with a median exposure to event of 12 weeks. Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories. Discontinuation due to weight gain occurred in 0.2% of olanzapine-treated patients and in 0% of placebo-treated patients.

In long-term studies (at least 48 weeks), the mean weight gain was 5.6 kg (12.3 lb) (median exposure of 573 days, N=2021). The percentages of patients who gained at least 7%, 15%, or 25% of their baseline body weight with long-term exposure were 64%, 32%, and 12%, respectively. Discontinuation due to weight gain occurred in 0.4% of olanzapine-treated patients following at least 48 weeks of exposure.

Table 6 includes data on adult weight gain with olanzapine pooled from 86 clinical trials. The data in each column represent data for those patients who completed treatment periods of the durations specified.

Table 6: Weight Gain with Olanzapine Use in Adults

Amount Gained kg (lb)	6 Weeks (N=7465) (%)	6 Months (N=4162) (%)	12 Months (N=1345) (%)	24 Months (N=474) (%)	36 Months (N=147) (%)
≤0	26.2	24.3	20.8	23.2	17.0
0 to ≤5 (0-11 lb)	57.0	36.0	26.0	23.4	25.2
>5 to ≤10 (11-22 lb)	14.9	24.6	24.2	24.1	18.4
>10 to ≤15 (22-33 lb)	1.8	10.9	14.9	11.4	17.0
>15 to ≤20 (33-44 lb)	0.1	3.1	8.6	9.3	11.6
>20 to ≤25 (44-55 lb)	0	0.9	3.3	5.1	4.1
>25 to ≤30 (55-66 lb)	0	0.2	1.4	2.3	4.8
>30 (>66 lb)	0	0.1	0.8	1.2	2

Olanzapine Monotherapy in Adolescents — The safety and efficacy of ZYPREXA RELPREV have not been established in patients under the age of 18 years.

Mean increase in weight in adolescents was greater than in adults. In 4 placebo-controlled trials, discontinuation due to weight gain occurred in 1% of olanzapine-treated patients, compared to 0% of placebo-treated patients.

Table 7: Weight Gain with Oral Olanzapine Use in Adolescents from 4 Placebo-Controlled Trials

	Olanzapine-treated patients	Placebo-treated patients
Mean change in body weight from baseline (median exposure = 3 weeks)	4.6 kg (10.1 lb)	0.3 kg (0.7 lb)
Percentage of patients who gained at least 7% of baseline body weight	40.6% (median exposure to 7% = 4 weeks)	9.8% (median exposure to 7% = 8 weeks)
Percentage of patients who gained at least 15% of baseline body weight	7.1% (median exposure to 15% = 19 weeks)	2.7% (median exposure to 15% = 8 weeks)

In long-term studies (at least 24 weeks), the mean weight gain was 11.2 kg (24.6 lb); (median exposure of 201 days, N=179). The percentages of adolescents who gained at least 7%, 15%, or 25% of their baseline body weight with long-term exposure were 89%, 55%, and 29%, respectively. Among adolescent patients, mean weight gain by baseline BMI category was 11.5 kg (25.3 lb), 12.1 kg (26.6 lb), and

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12.7 kg (27.9 lb), respectively, for normal (N=106), overweight (N=26) and obese (N=17). Discontinuation due to weight gain occurred in 2.2% of olanzapine-treated patients following at least 24 weeks of exposure.

Table 8 shows data on adolescent weight gain with olanzapine pooled from 6 clinical trials. The data in each column represent data for those patients who completed treatment periods of the durations specified. Little clinical trial data is available on weight gain in adolescents with olanzapine beyond 6 months of treatment.

Table 8: Weight Gain with Olanzapine Use in Adolescents

Amount Gained kg (lb)	6 Weeks (N=243) (%)	6 Months (N=191) (%)
<0	2.9	2.1
0 to ≤5 (0-11 lb)	47.3	24.6
>5 to ≤10 (11-22 lb)	42.4	26.7
>10 to ≤15 (22-33 lb)	5.8	22.0
>15 to ≤20 (33-44 lb)	0.8	12.6
>20 to ≤25 (44-55 lb)	0.8	9.4
>25 to ≤30 (55-66 lb)	0	2.1
>30 to ≤35 (66-77 lb)	0	0
>35 to ≤40 (77-88 lb)	0	0
>40 (>88 lb)	0	0.5

5.9 Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses or may even arise after discontinuation of treatment.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, olanzapine should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients (1) who suffer from a chronic illness that is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on olanzapine, drug discontinuation should be considered. However, some patients may require treatment with olanzapine despite the presence of the syndrome.

5.10 Orthostatic Hypotension

ZYPREXA RELPREV may induce orthostatic hypotension associated with dizziness, tachycardia, bradycardia and, in some patients, syncope, probably reflecting its α_1 -adrenergic antagonistic properties [see Patient Counseling Information (17.8)]. Syncope-related adverse reactions were reported in 0.1% of patients treated with ZYPREXA RELPREV in clinical studies.

Olanzapine should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications) where the occurrence of syncope, or hypotension and/or bradycardia might put the patient at increased medical risk. For patients in this population who have never taken oral olanzapine, tolerability should be established with oral olanzapine prior to initiating treatment with ZYPREXA RELPREV [see Dosage and Administration (2.1)].

Caution is necessary in patients who receive treatment with other drugs having effects that can induce hypotension, bradycardia, respiratory or central nervous system depression [see Drug Interactions (7)].

5.11 Leukopenia, Neutropenia, and Agranulocytosis

Class Effect — In clinical trial and/or postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including ZYPREXA. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of ZYPREXA RELPREV should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm³) should discontinue ZYPREXA RELPREV and have their WBC followed until recovery.

5.12 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's disease. Olanzapine is not approved for the treatment of patients with Alzheimer's disease.

5.13 Seizures

During premarketing testing of ZYPREXA RELPREV, seizures occurred in 0.15% of patients. During premarketing testing of oral olanzapine, seizures occurred in 0.9% of olanzapine-treated patients. There were confounding factors that may have contributed to the occurrence of seizures in many of these cases.

Olanzapine should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Olanzapine is not approved for the treatment of patients with Alzheimer's disease. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

5.14 Potential for Cognitive and Motor Impairment

Sedation was a commonly reported adverse reaction associated with ZYPREXA RELPREV treatment, occurring at an incidence of 8% in ZYPREXA RELPREV patients compared to 2% in placebo patients. Somnolence and sedation adverse reactions led to discontinuation in 0.6% of patients in the premarketing ZYPREXA RELPREV database.

Since olanzapine has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that olanzapine therapy does not affect them adversely. However, due to the risk of post-injection delirium/sedation syndrome after each injection, patients should not drive or operate heavy machinery for the remainder of the day of each injection [see Dosage and Administration (2.1), Warnings and Precautions (5.1), and Patient Counseling Information (17.9)].

5.15 Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing ZYPREXA RELPREV for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration [see Patient Counseling Information (17.10)].

5.16 Use in Patients with Concomitant Illness

Experience with ZYPREXA RELPREV in patients with concomitant systemic illnesses is limited [see Clinical Pharmacology (12.3)].

Olanzapine exhibits in vitro muscarinic receptor affinity. In premarketing clinical trials with oral olanzapine, olanzapine was associated with constipation, dry mouth, and tachycardia, all adverse reactions possibly related to cholinergic antagonism. Such adverse reactions were not often the basis for discontinuations from olanzapine, but olanzapine should be used with caution in patients with clinically significant prostatic hypertrophy, narrow angle glaucoma, or a history of paralytic ileus or related conditions.

In 5 placebo-controlled studies of oral olanzapine in elderly patients with dementia-related psychosis (n=1184), the following treatment-emergent adverse reactions were reported in olanzapine-treated patients at an incidence of at least 2% and significantly greater than placebo-treated patients: falls, somnolence, peripheral edema, abnormal gait, urinary incontinence, lethargy, increased weight, asthenia, pyrexia, pneumonia, dry mouth and visual hallucinations. The rate of discontinuation due to adverse reactions was significantly greater with oral olanzapine than placebo (13% vs 7%). Elderly patients with dementia-related psychosis treated with olanzapine are at an increased risk of death compared to placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis [see Boxed Warning, Warnings and Precautions (5.3), and Patient Counseling Information (17.11)].

Olanzapine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with olanzapine, caution should be observed in cardiac patients [see Warnings and Precautions (5.10)].

5.17 Hyperprolactinemia

As with other drugs that antagonize dopamine D₂ receptors, olanzapine elevates prolactin levels, and the elevation persists during chronic administration. Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. As is common with compounds which increase prolactin release, an increase in mammary gland neoplasia was observed in the oral olanzapine carcinogenicity studies conducted in mice and rats [see Nonclinical Toxicology (13.1)]. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time. In premarketing studies with ZYPREXA RELPREV, statistically significant differences among dose groups have been observed for prolactin levels [see Adverse Reactions (6.1)].

In placebo-controlled olanzapine clinical studies (up to 12 weeks), changes from normal to high in prolactin concentrations were observed in 30% of adults treated with olanzapine as compared to 10.5% of adults treated with placebo. In a pooled analysis from clinical studies including 8136 adults treated with olanzapine, potentially associated clinical manifestations included menstrual-related events¹ (2% [49/3240] of females), sexual function-related events² (2% [150/8136] of females and males), and breast-related events³ (0.7% [23/3240] of females, 0.2% [9/4896] of males).

In placebo-controlled olanzapine monotherapy studies in adolescent patients (up to 6 weeks) with schizophrenia or bipolar I disorder (manic or mixed episodes), changes from normal to high in prolactin concentrations were observed in 47% of olanzapine-treated patients compared to 7% of placebo-treated patients. In a pooled analysis from clinical trials including 454 adolescents treated with olanzapine, potentially associated clinical manifestations included menstrual-related events¹ (1% [2/168] of females), sexual function-related events² (0.7% [3/454] of females and males), and breast-related events³ (2% [3/168] of females, 2% [7/286] of males) [see Use in Specific Populations (8.4)].

¹ Based on a search of the following terms: amenorrhea, hypomenorrhea, menstruation delayed, and oligomenorrhea.

² Based on a search of the following terms: anorgasmia, delayed ejaculation, erectile dysfunction, decreased libido, loss of libido, abnormal orgasm, and sexual dysfunction.

³ Based on a search of the following terms: breast discharge, enlargement or swelling, galactorrhea, gynecomastia, and lactation disorder.

5.18 Laboratory Tests

Fasting blood glucose testing and lipid profile at the beginning of, and periodically during, treatment is recommended [see Warnings and Precautions (5.6, 5.7) and Patient Counseling Information (17.4, 17.5)].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The information below for ZYPREXA RELPREV is derived primarily from a clinical trial database consisting of 2058 patients with approximately 1948 patient years of exposure to ZYPREXA RELPREV. This database includes safety data from 6 open-label studies and 2 double-blind comparator studies, conducted in patients with schizophrenia or schizoaffective disorder. Additionally, data obtained from patients treated with oral olanzapine are also presented below. Adverse reactions were assessed by the collection of adverse reactions, vital signs, weights, laboratory analytes, ECGs, and the results of physical and ophthalmologic examinations. In the tables and tabulations that follow for ZYPREXA RELPREV, the MedDRA terminology has been used to classify reported adverse reactions. Data obtained from oral olanzapine studies was reported using the COSTART dictionary.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse reaction of the type listed. A reaction was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. Reactions listed elsewhere in labeling may not be repeated below. The entire label should be read to gain a complete understanding of the safety profile of ZYPREXA RELPREV.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited

figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse reaction incidence in the population studied.

Adverse Reactions Associated with Discontinuation of Treatment in a Short-Term, Placebo-Controlled Trial
Overall, there was no difference in the incidence of discontinuation due to adverse reactions between ZYPREXA RELPREVV (4%; 13/306 patients) and placebo (5%; 5/98 patients) in an 8-week trial.

Commonly Observed Adverse Reactions in a Short-Term, Placebo-Controlled Trial
In an 8-week trial, treatment-emergent adverse reactions with an incidence of 5% or greater in at least one of the ZYPREXA RELPREVV treatment groups (210 mg/2 weeks, 405 mg/4 weeks, or 300 mg/2 weeks) and greater than placebo were: headache, sedation, weight gain, cough, diarrhea, back pain, nausea, somnolence, dry mouth, nasopharyngitis, increased appetite, and vomiting.

Adverse Reactions Occurring at an Incidence of 2% or More among ZYPREXA RELPREVV-Treated Patients in a Short-Term, Placebo-Controlled Trial

Table 9 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred in 2% or more of patients treated with ZYPREXA RELPREVV and with incidence greater than placebo who participated in the 8-week, placebo-controlled trial.

Table 9: Treatment-Emergent Adverse Reactions: Incidence in a Short-Term, Placebo-Controlled Clinical Trial with ZYPREXA RELPREVV

Body System/Adverse Reaction	Percentage of Patients Reporting Adverse Event			
	Placebo (N=98)	ZYPREXA RELPREVV 405 mg/4 wks (N=100)	ZYPREXA RELPREVV 210 mg/2 wks (N=106)	ZYPREXA RELPREVV 300 mg/2 wks (N=100)
Ear and Labyrinth Disorders				
Ear pain	2	1	1	4
Gastrointestinal Disorders				
Abdominal pain ^a	2	3	3	3
Diarrhea	4	2	7	5
Dry mouth	1	2	6	4
Flatulence	0	2	2	1
Nausea	2	5	5	4
Toothache	0	3	4	3
Vomiting	2	6	1	2
General Disorders and Administration				
Site Conditions				
Fatigue	2	4	2	3
Injection site pain	0	2	3	2
Pain	0	0	2	3
Pyrexia	0	2	0	0
Infections and Infestations				
Nasopharyngitis	2	3	6	1
Tooth infection ^b	0	4	0	0
Upper respiratory tract infection	2	3	1	4
Viral infection	0	0	0	2
Injury, Poisoning and Procedural Complications				
Procedural pain	0	2	0	0
Investigations				
Electrocardiogram QT-corrected interval prolonged	1	0	0	2
Hepatic enzyme increased ^c	1	4	1	3
Weight increased	5	5	6	7
Metabolism and Nutrition Disorders				
Increased appetite	0	1	4	6
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	0	3	3	3
Back pain	4	4	3	5
Muscle spasms	0	3	1	2
Musculoskeletal stiffness	1	1	4	4
Nervous System Disorders				
Dizziness	2	4	4	1
Dysarthria	0	0	1	2
Headache ^d	8	13	15	18
Sedation ^e	7	13	8	13
Tremor	1	3	0	1
Psychiatric Disorders				
Abnormal dreams	0	0	0	2
Hallucination, auditory	2	3	1	0
Restlessness	2	2	3	1
Sleep disorder	1	0	0	2
Thinking abnormal	1	3	0	0
Reproductive System and Breast Disorders				
Vaginal discharge	0	0	4	4
Respiratory, Thoracic and Mediastinal Disorders				
Cough	5	3	5	9
Nasal congestion ^f	3	2	1	7
Pharyngolaryngeal pain	2	2	3	3
Sneezing	0	0	0	2
Skin and Subcutaneous Tissue Disorders				
Acne	0	2	0	2
Vascular Disorders				
Hypertension	0	3	2	0

^a The term abdominal pain upper was combined under abdominal pain.

^b The term tooth abscess was combined under tooth infection.

^c The terms alanine aminotransferase increased, aspartate aminotransferase increased, and gamma-glutamyltransferase increased were combined under hepatic enzyme increased.

^d The term tension headache was combined under headache.

^e The term somnolence was combined under sedation.

^f The term sinus congestion was combined under nasal congestion.

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Summary of Statistically Significant Changes by Dose

In a 24-week randomized, double-blind, fixed-dose study comparing 3 doses of ZYPREXA RELPREVV in patients with schizophrenia, statistically significant differences among dose groups were observed for the below safety outcomes (Table 10) [see *Warnings and Precautions* (5.8, 5.17)].

Table 10: Summary of Statistically Significant Changes by Dose in a Double-Blind, Fixed-Dose Study for ZYPREXA RELPREVV^a

	ZYPREXA RELPREVV Dose		
	150 mg/2 weeks	405 mg/4 weeks	300 mg/2 weeks
Weight: mean change in kg (N ^b)	0.67 (140)	0.89 (315)	1.70 ^b (140)
Prolactin: mean change in µg/L (N ^b)	-5.61 (109)	-2.76 (259)	3.57 ^{b,c} (115)
Fasting triglycerides: patients who met the criteria ^d for change from normal at baseline to high at anytime n/N ² (%)	4/62 (6.5)	13/133 (9.8)	13/53 ^{b,c} (24.5)

^a Abbreviations: N¹=Number of patients who have both baseline and post-baseline measurement; n=number of patients with an abnormal post-baseline measurement at any time; N²=Number of patients with a normal baseline and at least one post-baseline measurement.

^b p<0.05 versus 150 mg/2 weeks ZYPREXA RELPREVV; pairwise p-values.

^c p<0.05 versus 405 mg/4 weeks ZYPREXA RELPREVV; pairwise p-values.

^d Triglycerides normal to high limits are <150 mg/dL to 200 mg/dL ≤X<500 mg/dL.

Dose Dependency of Adverse Reactions in Short-Term, Placebo-Controlled Trials

Extrapyramidal Symptoms: The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by categorical analyses of formal rating scales during acute therapy in a controlled clinical trial comparing oral olanzapine at 3 fixed doses with placebo in the treatment of schizophrenia in a 6-week trial.

Table 11: Treatment-Emergent Extrapyramidal Symptoms Assessed by Rating Scales Incidence in a Fixed Dosage Range, Placebo-Controlled Clinical Trial of Oral Olanzapine in Schizophrenia — Acute Phase

	Percentage of Patients Reporting Event			
	Placebo	Olanzapine 5 ± 2.5 mg/day	Olanzapine 10 ± 2.5 mg/day	Olanzapine 15 ± 2.5 mg/day
Parkinsonism ^a	15	14	12	14
Akathisia ^b	23	16	19	27

^a Percentage of patients with a Simpson-Angus Scale total score >3.

^b Percentage of patients with a Barnes Akathisia Scale global score ≥2.

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse reactions during acute therapy in the same controlled clinical trial comparing olanzapine at 3 fixed doses with placebo in the treatment of schizophrenia in a 6-week trial.

Table 12: Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Reactions Incidence in a Fixed Dosage Range, Placebo-Controlled Clinical Trial of Oral Olanzapine in Schizophrenia — Acute Phase

	Percentage of Patients Reporting Event			
	Placebo (N=68)	Olanzapine 5 ± 2.5 mg/day (N=65)	Olanzapine 10 ± 2.5 mg/day (N=64)	Olanzapine 15 ± 2.5 mg/day (N=69)
Dystonic events ^a	1	3	2	3
Parkinsonism events ^b	10	8	14	20
Akathisia events ^c	1	5	11	10
Dyskinetic events ^d	4	0	2	1
Residual events ^e	1	2	5	1
Any extrapyramidal event	16	15	25	32

^a Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis.

^b Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor.

^c Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.

^d Patients with the following COSTART terms were counted in this category: buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia.

^e Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching.

Dystonia, Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, the frequency and severity are greater with high potency and at higher doses of first generation antipsychotic drugs. In general, an elevated risk of acute dystonia may be observed in males and younger age groups receiving antipsychotics; however, events of dystonia have been reported infrequently (<1%) with olanzapine use.

Differences among Fixed-Dose Groups Observed in Oral Olanzapine Clinical Trials

In a single 8-week randomized, double-blind, fixed-dose study comparing 10 (N=199), 20 (N=200) and 40 (N=200) mg/day of oral olanzapine in patients with schizophrenia or schizoaffective disorder, differences among 3 dose groups were observed for the following safety outcomes: weight gain, prolactin elevation, fatigue and dizziness. Mean baseline to endpoint increase in weight (10 mg/day: 1.9 kg; 20 mg/day: 2.3 kg; 40 mg/day: 3 kg) was observed with significant differences between 10 vs 40 mg/day. Incidence of treatment-emergent prolactin elevation >24.2 ng/mL (female) or >18.77 ng/mL (male) at any time during the trial (10 mg/day: 31.2%; 20 mg/day: 42.7%; 40 mg/day: 61.1%) with significant differences between 10 vs 40 mg/day and 20 vs 40 mg/day; fatigue (10 mg/day: 1.5%; 20 mg/day: 2.1%; 40 mg/day: 6.6%) with significant differences between 10 vs 40 and 20 vs 40 mg/day; and dizziness (10 mg/day: 2.6%; 20 mg/day: 1.6%; 40 mg/day: 6.6%) with significant differences between 20 vs 40 mg, was observed.

Local Injection Site Reactions

Eleven ZYPREXA RELPREVV-treated patients (3.6%) and 0 placebo-treated patients experienced treatment-emergent injection-related adverse reactions (injection site pain, buttock pain, injection site mass, induration, injection site induration) in the placebo-controlled database. The most frequently occurring treatment-emergent adverse reaction was injection site pain (2.3% ZYPREXA RELPREVV-treated; 0% placebo-treated).

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Commonly Observed Adverse Reactions During the Clinical Trial Evaluation of Oral Olanzapine

In clinical trials of oral olanzapine monotherapy for the treatment of schizophrenia in adult patients, treatment-emergent adverse reactions with an incidence of 5% or greater in the olanzapine treatment arm and at least twice that of placebo were: postural hypotension, constipation, weight gain, dizziness, personality disorder, and akathisia.

Other Adverse Reactions Observed During the Clinical Trial Evaluation of Oral Olanzapine

Following is a list of treatment-emergent adverse reactions reported by patients treated with oral olanzapine (at multiple doses ≥ 1 mg/day) in clinical trials. This listing is not intended to include reactions (1) already listed in previous tables or elsewhere in labeling, (2) for which a drug cause was remote, (3) which were so general as to be uninformative, (4) which were not considered to have significant clinical implications, or (5) which occurred at a rate equal to or less than placebo. Reactions are classified by body system using the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare adverse reactions are those occurring in fewer than 1/1000 patients.

Body as a Whole — *Infrequent:* chills, face edema, photosensitivity reaction, suicide attempt¹; *Rare:* chills and fever, hangover effect, sudden death¹.

Cardiovascular System — *Infrequent:* cerebrovascular accident, vasodilatation.

Digestive System — *Infrequent:* nausea and vomiting, tongue edema; *Rare:* ileus, intestinal obstruction, liver fatty deposit.

Hemic and Lymphatic System — *Infrequent:* leukopenia, thrombocytopenia.

Metabolic and Nutritional Disorders — *Infrequent:* alkaline phosphatase increased, bilirubinemia, hypoproteinemia.

Musculoskeletal System — *Rare:* osteoporosis.

Nervous System — *Infrequent:* ataxia, dysarthria, libido decreased, stupor; *Rare:* coma.

Respiratory System — *Infrequent:* epistaxis; *Rare:* lung edema.

Skin and Appendages — *Infrequent:* alopecia.

Special Senses — *Infrequent:* abnormality of accommodation, dry eyes; *Rare:* mydriasis.

Urogenital System — *Infrequent:* amenorrhea², breast pain, decreased menstruation, impotence², increased menstruation², menorrhagia², metrorrhagia², polyuria², urinary frequency, urinary retention, urinary urgency, urination impaired.

¹ These terms represent serious adverse events but do not meet the definition for adverse drug reactions. They are included here because of their seriousness.

² Adjusted for gender.

6.2 Vital Signs and Laboratory Studies

Laboratory Changes

ZYPREXA RELPREV in Adults: Statistically significant within group mean changes for ZYPREXA RELPREV, which were also significantly different from placebo, were observed for the following: eosinophils, monocytes, cholesterol, low-density lipoprotein (LDL), triglycerides, and direct bilirubin. There were no statistically significant differences between ZYPREXA RELPREV and placebo in the incidence of potentially clinically significant changes in any of the laboratory values studied.

Statistically significant within group mean changes for ZYPREXA RELPREV, which were also significantly different from oral olanzapine (in a 24-week double-blind study), were observed for the following: gamma-glutamyltransferase (GGT) and sodium. Statistically significant differences were observed between ZYPREXA RELPREV and oral olanzapine for the incidence of treatment-emergent low platelet count (0% ZYPREXA RELPREV vs 1% oral olanzapine); and low total bilirubin (2.8% ZYPREXA RELPREV vs 0.7% for oral olanzapine). There was a statistically significant difference between ZYPREXA RELPREV and oral olanzapine in potentially clinically significant changes for high leukocyte count (0% ZYPREXA RELPREV vs 1% oral olanzapine).

Changes in aminotransferases observed with ZYPREXA RELPREV treatment were similar to those reported with ZYPREXA treatment. In placebo-controlled ZYPREXA RELPREV studies, clinically significant ALT elevations (≥ 3 times the upper limit of the normal range) were observed in 2.7% (8/291) of patients exposed to olanzapine compared to 3.2% (3/94) of the placebo patients. None of these patients experienced jaundice. In 3 of these patients, liver enzymes reverted to the normal range despite continued treatment, and in 5 cases enzymes values decreased, but were still above the normal range at the end of therapy.

Within the larger premarketing ZYPREXA RELPREV database of 1886 patients with baseline ALT ≤ 90 IU/L, the incidence of ALT elevation to >200 IU/L was 0.8%. None of these patients experienced jaundice or other symptoms attributable to liver impairment and most had transient changes that tended to normalize while ZYPREXA RELPREV treatment was continued.

Olanzapine Monotherapy in Adults: An assessment of the premarketing experience for oral olanzapine revealed an association with asymptomatic increases in ALT, AST, and GGT. Within the original premarketing database of about 2400 adult patients with baseline ALT ≤ 90 IU/L, the incidence of ALT elevations to >200 IU/L was 2% (50/2381). None of these patients experienced jaundice or other symptoms attributable to liver impairment and most had transient changes that tended to normalize while olanzapine treatment was continued.

In placebo-controlled oral olanzapine monotherapy studies in adults, clinically significant ALT elevations (change from <3 times the upper limit of normal [ULN] at baseline to ≥ 3 times ULN) were observed in 5% (77/1426) of patients exposed to olanzapine compared to 1% (10/1187) of patients exposed to placebo. ALT elevations ≥ 5 times ULN were observed in 2% (29/1438) of olanzapine-treated patients, compared to 0.3% (4/1196) of placebo-treated patients. ALT values returned to normal, or were decreasing, at last follow-up in the majority of patients who either continued treatment with olanzapine or discontinued olanzapine. No patient with elevated ALT values experienced jaundice, liver failure, or met the criteria for Hy's Rule.

Rare postmarketing reports of hepatitis have been received for patients taking different formulations of olanzapine. Very rare cases of cholestatic or mixed liver injury have also been reported in the postmarketing period.

Caution should be exercised in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic drugs.

Oral olanzapine administration was also associated with increases in serum prolactin [see *Warnings and Precautions (5.17)*], with an asymptomatic elevation of the eosinophil count in 0.3% of patients, and with an increase in CPK.

ECG Changes — Comparison of ZYPREXA RELPREV and oral olanzapine, in a 24 week study, revealed no significant differences on ECG changes. Between-group comparisons for pooled placebo-controlled trials revealed no significant oral olanzapine/placebo differences in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. Oral olanzapine use was

associated with a mean increase in heart rate of 2.4 beats per minute compared to no change among placebo patients. This slight tendency to tachycardia may be related to olanzapine's potential for inducing orthostatic changes [see *Warnings and Precautions (5.11)*].

6.3 Postmarketing Experience

Adverse reactions reported since market introduction that were temporally (but not necessarily causally) related to ZYPREXA therapy include the following: allergic reaction (e.g., anaphylactoid reaction, angioedema, pruritus or urticaria), diabetic coma, diabetic ketoacidosis, discontinuation reaction (diaphoresis, nausea, or vomiting), jaundice, neutropenia, pancreatitis, priapism, rash, rhabdomyolysis, and venous thromboembolic events (including pulmonary embolism and deep venous thrombosis). Random cholesterol levels of ≥ 240 mg/dL and random triglyceride levels of ≥ 1000 mg/dL have been reported.

7 DRUG INTERACTIONS

7.1 Potential for Other Drugs to Affect Olanzapine

Diazepam — The co-administration of diazepam with olanzapine potentiated the orthostatic hypotension observed with olanzapine [see *Drug Interactions (7.2)*].

Inducers of CYP1A2 — Carbamazepine therapy (200 mg bid) causes an approximately 50% increase in the clearance of olanzapine. This increase is likely due to the fact that carbamazepine is a potent inducer of CYP1A2 activity. Higher daily doses of carbamazepine may cause an even greater increase in olanzapine clearance.

Alcohol — Ethanol (45 mg/70 kg single dose) did not have an effect on olanzapine pharmacokinetics. The co-administration of alcohol (i.e., ethanol) with olanzapine potentiated the orthostatic hypotension observed with olanzapine [see *Drug Interactions (7.2)*].

Inhibitors of CYP1A2 — Fluvoxamine, a CYP1A2 inhibitor, decreases the clearance of olanzapine. This results in a mean increase in olanzapine C_{max} following fluvoxamine of 54% in female nonsmokers and 77% in male smokers. The mean increase in olanzapine AUC is 52% and 108%, respectively. Lower doses of olanzapine should be considered in patients receiving concomitant treatment with fluvoxamine.

Inhibitors of CYP2D6 — Fluoxetine caused a small decrease in olanzapine clearance leading to a minimal change in olanzapine steady-state concentrations and, therefore dose modification is not routinely recommended.

Warfarin — Warfarin (20 mg single dose) did not affect olanzapine pharmacokinetics [see *Drug Interactions (7.2)*].

Inducers of CYP1A2 or Glucuronyl Transferase Enzymes — Omeprazole and rifampin may cause an increase in olanzapine clearance.

7.2 Potential for Olanzapine to Affect Other Drugs

CNS Acting Drugs — Given the primary CNS effects of olanzapine, caution should be used when olanzapine is taken in combination with other centrally acting drugs and alcohol.

Antihypertensive Agents — Olanzapine, because of its potential for inducing hypotension, may enhance the effects of certain antihypertensive agents.

Levodopa and Dopamine Agonists — Olanzapine may antagonize the effects of levodopa and dopamine agonists.

Lorazepam (LM) — Co-administration of lorazepam does not significantly affect the pharmacokinetics of olanzapine, unconjugated lorazepam, or total lorazepam. However, this co-administration of lorazepam with olanzapine potentiated the somnolence observed with either drug alone.

Lithium — Multiple doses of olanzapine (10 mg for 8 days) did not influence the kinetics of lithium. Therefore, concomitant olanzapine administration does not require dosage adjustment of lithium.

Valproate — Olanzapine (10 mg daily for 2 weeks) did not affect the steady-state plasma concentrations of valproate. Therefore, concomitant olanzapine administration does not require dosage adjustment of valproate.

Effect of Olanzapine on Drug Metabolizing Enzymes — In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.

Imipramine — Single doses of olanzapine did not affect the pharmacokinetics of imipramine or its active metabolite desipramine.

Warfarin — Single doses of olanzapine did not affect the pharmacokinetics of warfarin [see *Drug Interactions (7.1)*].

Diazepam — Olanzapine did not influence the pharmacokinetics of diazepam or its active metabolite N-desmethyldiazepam. However, diazepam co-administered with olanzapine increased the orthostatic hypotension observed with either drug given alone [see *Drug Interactions (7.1)*].

Alcohol — Multiple doses of olanzapine did not influence the kinetics of ethanol [see *Drug Interactions (7.1)*].

Biperiden — Multiple doses of olanzapine did not influence the kinetics of biperiden.

Theophylline — Multiple doses of olanzapine did not affect the pharmacokinetics of theophylline or its metabolites.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects, Pregnancy Category C — In oral reproduction studies in rats at doses up to 18 mg/kg/day and in rabbits at doses up to 30 mg/kg/day (9 and 30 times the maximum recommended human daily oral dose on a mg/m² basis, respectively) no evidence of teratogenicity was observed. In an oral rat teratology study, early resorptions and increased numbers of nonviable fetuses were observed at a dose of 18 mg/kg/day (9 times the maximum recommended human daily oral dose on a mg/m² basis). Gestation was prolonged at 10 mg/kg/day (5 times the maximum recommended human daily oral dose on a mg/m² basis). In an oral rabbit teratology study, fetal toxicity (manifested as increased resorptions and decreased fetal weight) occurred at a maternally toxic dose of 30 mg/kg/day (30 times the maximum recommended human daily oral dose on a mg/m² basis). No evidence of teratogenicity or embryo-fetal toxicity was observed in rats or rabbits with ZYPREXA RELPREV at intramuscular doses up to 75 mg/kg (1 and 2 times the maximum recommended human dose of 300 mg every 2 weeks, respectively, on a mg/m² basis). Placental transfer of olanzapine occurred in rat pups.

There are no adequate and well-controlled trials with olanzapine in pregnant females. Four pregnancies were observed during clinical trials with ZYPREXA RELPREV, including 1 resulting in a normal birth and 3 therapeutic abortions. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects — Neonates exposed to antipsychotic drugs (including olanzapine), during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

ZYPREXA RELPREW should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.2 Labor and Delivery

The effect of olanzapine on labor and delivery in humans is unknown. Parturition in rats was not affected by olanzapine.

8.3 Nursing Mothers

In an oral olanzapine study in lactating, healthy women, olanzapine was excreted in breast milk. Mean infant dose at steady state was estimated to be 1.8% of the maternal olanzapine dose. It is recommended that women receiving ZYPREXA RELPREW should not breast-feed.

8.4 Pediatric Use

Safety and effectiveness of ZYPREXA RELPREW in children and adolescent patients have not been established [see *Warnings and Precautions* (5.6, 5.7, 5.8)].

Compared to patients from adult clinical trials, adolescents treated with oral ZYPREXA were likely to gain more weight, experience increased sedation, and have greater increases in total cholesterol, triglycerides, LDL cholesterol, prolactin and hepatic aminotransferase levels.

8.5 Geriatric Use

Clinical studies of ZYPREXA RELPREW did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In the premarketing clinical studies with oral olanzapine, there was no indication of any different tolerability of olanzapine in elderly patients compared to younger patients with schizophrenia. Oral olanzapine studies in elderly patients with dementia-related psychosis have suggested that there may be a different tolerability profile in this population compared to younger patients with schizophrenia. Elderly patients with dementia-related psychosis treated with olanzapine are at an increased risk of death compared to placebo. In placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis, there was a higher incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis. Also, the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to olanzapine should lead to consideration of a lower starting dose for any geriatric patient [see *Boxed Warning, Warnings and Precautions* (5.3), and *Dosage and Administration* (2.1)].

9 DRUG ABUSE AND DEPENDENCE

9.3 Dependence

In studies prospectively designed to assess abuse and dependence potential, olanzapine was shown to have acute depressive CNS effects but little or no potential of abuse or physical dependence in rats administered oral doses up to 15 times the maximum recommended human daily oral dose (20 mg) and rhesus monkeys administered oral doses up to 8 times the maximum recommended human daily oral dose on a mg/m² basis.

Olanzapine has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. Because ZYPREXA RELPREW is to be administered by healthcare professionals, the potential for misuse or abuse by patients is low.

10 OVERDOSAGE

10.1 Human Experience

During premarketing clinical studies of ZYPREXA RELPREW, adverse reactions that presented with signs and symptoms consistent with olanzapine overdose, in particular, sedation (including coma) and/or delirium, were reported in patients following an injection of ZYPREXA RELPREW [see *Boxed Warning and Dosage and Administration* (2.1)]. These reactions occurred in <0.1% of injections and in approximately 2% of patients who received injections for up to 46 months. These reactions were correlated with an unintentional rapid increase in serum olanzapine concentrations to supra-therapeutic ranges in some cases. While a rapid and greater than expected increase in serum olanzapine concentration has been observed in some patients with these reactions, the exact mechanism by which the drug was unintentionally introduced into the blood stream is not known. Clinical signs and symptoms included dizziness, confusion, disorientation, slurred speech, altered gait, difficulty ambulating, weakness, agitation, extrapyramidal symptoms, hypertension, convulsion, and reduced level of consciousness ranging from mild sedation to coma. Time after injection to event ranged from soon after injection to greater than 3 hours after injection. The majority of patients were hospitalized and some required supportive care, including intubation, in several cases. All patients had largely recovered by 72 hours. The risk of an event is the same at each injection, so the risk per patient is cumulative (i.e., increases with the number of injections) [see *Warnings and Precautions* (5.1)].

In postmarketing reports of overdose with oral olanzapine alone, symptoms have been reported in the majority of cases. In symptomatic patients, symptoms with ≥10% incidence included agitation/aggressiveness, dysarthria, tachycardia, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma. Among less commonly reported symptoms were the following potentially medically serious reactions: aspiration, cardiopulmonary arrest, cardiac arrhythmias (such as supraventricular tachycardia and 1 patient experiencing sinus pause with spontaneous resumption of normal rhythm), delirium, possible neuroleptic malignant syndrome, respiratory depression/arrest, convulsion, hypertension, and hypotension. Eli Lilly and Company has received reports of fatality in association with overdose of oral olanzapine alone. In 1 case of death, the amount of acutely ingested oral olanzapine was reported to be possibly as low as 450 mg of oral olanzapine; however, in another case, a patient was reported to survive an acute olanzapine ingestion of approximately 2 g of oral olanzapine.

10.2 Management of Overdose

Post-injection delirium/sedation syndrome may occur with each injection of ZYPREXA RELPREW. Signs and symptoms consistent with olanzapine overdose have been observed, and access to emergency response services must be readily available for safe use [see *Boxed Warning and Warnings and Precautions* (5.1)].

There is no specific antidote to olanzapine. Therefore, appropriate supportive measures should be initiated. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. (Do not use epinephrine, dopamine, or other sympathomimetics with beta-agonist activity, since beta stimulation may worsen hypotension in the setting of olanzapine-induced alpha blockade.) Respiratory support, including ventilation, may be required. Close medical supervision and monitoring should continue until the patient recovers.

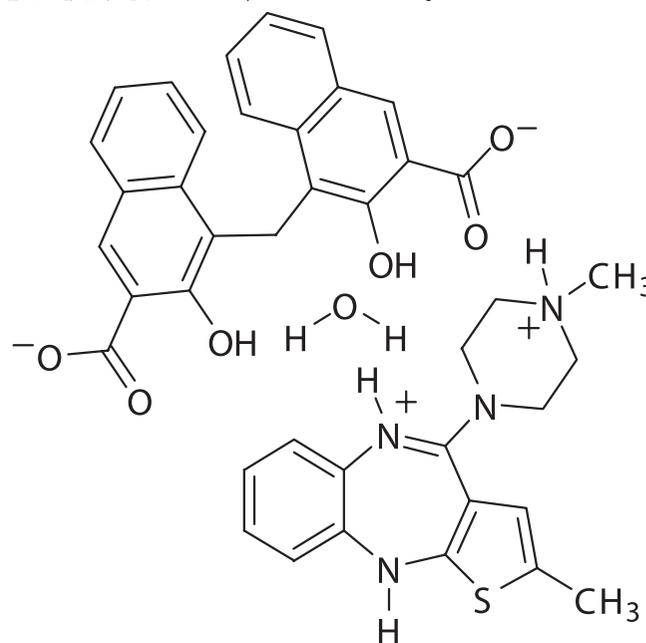
The possibility of multiple drug involvement should be considered. In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation, which may include intubation. The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

ZYPREXA RELPREW (olanzapine) For Extended Release Injectable Suspension

PV 5924 AMP

11 DESCRIPTION

ZYPREXA RELPREW is an atypical antipsychotic that belongs to the thienobenzodiazepine class. The chemical designation is 10H-thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)-, 4,4'-methylenebis[3-hydroxy-2-naphthalenecarboxylate] (1:1), monohydrate. The formula is C₁₇H₂₂N₄S•C₂₃H₁₄O₆•H₂O, which corresponds to a molecular weight of 718.8. The chemical structure is:



ZYPREXA RELPREW is a long-acting form of olanzapine and is intended for deep intramuscular gluteal injection only.

ZYPREXA RELPREW includes a vial of the drug product and a vial of the sterile diluent for ZYPREXA RELPREW.

The drug product is olanzapine pamoate monohydrate, present as a yellow solid in a glass vial equivalent to 210, 300, or 405 mg olanzapine base per vial. The diluent for ZYPREXA RELPREW is a clear, colorless to slightly yellow solution in a glass vial and is composed of carboxymethylcellulose sodium, mannitol, polysorbate 80, sodium hydroxide and/or hydrochloric acid for pH adjustment, and water for injection. The drug product is suspended in the diluent for ZYPREXA RELPREW to a target concentration of 150 mg olanzapine per mL prior to intramuscular injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of olanzapine, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine and serotonin type 2 (5HT₂) antagonism.

12.2 Pharmacodynamics

Olanzapine binds with high affinity to the following receptors: serotonin 5HT_{2A/2C}, 5HT₆ (K_i=4, 11, and 5 nM, respectively), dopamine D_{1,4} (K_i=11-31 nM), histamine H₁ (K_i=7 nM), and adrenergic α₁ receptors (K_i=19 nM). Olanzapine is an antagonist with moderate affinity binding for serotonin 5HT₃ (K_i=57 nM) and muscarinic M₁₋₅ (K_i=73, 96, 132, 32, and 48 nM, respectively). Olanzapine binds weakly to GABA_A, BZD, and β-adrenergic receptors (K_i>10 μM).

Antagonism at receptors other than dopamine and 5HT₂ may explain some of the other therapeutic and side effects of olanzapine. Olanzapine's antagonism of muscarinic M₁₋₅ receptors may explain its anticholinergic-like effects. Olanzapine's antagonism of histamine H₁ receptors may explain the somnolence observed with this drug. Olanzapine's antagonism of adrenergic α₁ receptors may explain the orthostatic hypotension observed with this drug.

12.3 Pharmacokinetics

The fundamental pharmacokinetic properties of olanzapine are similar for ZYPREXA RELPREW and orally administered olanzapine. Refer to the section below describing the pharmacokinetics of orally administered olanzapine for details.

Slow dissolution of ZYPREXA RELPREW, a practically insoluble salt, after a deep intramuscular gluteal injection of a dose of ZYPREXA RELPREW results in prolonged systemic olanzapine plasma concentrations that are sustained over a period of weeks to months. An injection every 2 or 4 weeks provides olanzapine plasma concentrations that are similar to those achieved by daily doses of oral olanzapine. The steady-state plasma concentrations for ZYPREXA RELPREW for doses of 150 mg to 405 mg every 2 or 4 weeks are within the range of steady-state olanzapine plasma concentration known to have been associated with oral doses of 5 mg to 20 mg olanzapine once daily. The change to a slow release, rate-controlled absorption process is the only fundamental pharmacokinetic difference between the administration of ZYPREXA RELPREW and orally administered olanzapine. The effective half-life for olanzapine after intramuscular ZYPREXA RELPREW administration is approximately 30 days as compared to a half-life after oral administration of approximately 30 hours. Exposure to olanzapine may persist for a period of months after a ZYPREXA RELPREW injection. The long persistence of systemic concentrations of olanzapine may be an important consideration for the long-term clinical management of the patient. Typical systemic olanzapine plasma concentrations reach a peak within the first week after injection and are at trough level immediately prior to the next injection. The olanzapine plasma concentration fluctuation between the peak and trough is comparable to the peak and trough fluctuations associated with once daily oral dosing.

Dose Proportionality and Oral Dose Correspondence — ZYPREXA RELPREW provides a dose of 150, 210, 300, or 405 mg olanzapine. An injection of a larger dose produces a dose-proportional increase in the systemic exposure. The olanzapine exposure after doses of ZYPREXA RELPREW corresponds to exposure for oral doses of olanzapine. A ZYPREXA RELPREW dose of 300 mg olanzapine injected every two weeks delivers approximately 20 mg olanzapine per day and a ZYPREXA RELPREW dose of 150 mg olanzapine injected every two weeks delivers approximately 10 mg per day. These ZYPREXA RELPREW doses sustain steady-state olanzapine concentrations over long periods of treatment.

ZYPREXA RELPREW (olanzapine) For Extended Release Injectable Suspension

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Pharmacokinetic Impact of Switching to ZYPREXA RELPREV from Oral Olanzapine — The switch from oral olanzapine to ZYPREXA RELPREV changes the pharmacokinetics from an elimination-rate-controlled to an absorption-rate-controlled process. The switch to ZYPREXA RELPREV may require treatment for a period of approximately 3 months to re-establish steady-state conditions. Initial treatment with ZYPREXA RELPREV is recommended at a dose corresponding to the mg/day oral dose [see *Dosage and Administration* (2.1)]. Plasma concentrations of olanzapine during the first injection interval may be lower than those maintained by a corresponding oral dose. Even though the concentrations are lower, the olanzapine concentrations remained within a therapeutically effective range and supplementation with orally administered olanzapine was generally not necessary in clinical trials.

Olanzapine is extensively distributed throughout the body, with a volume of distribution of approximately 1000 L. It is 93% bound to plasma proteins over the concentration range of 7 to 1100 ng/mL, binding primarily to albumin and α_1 -acid glycoprotein.

Metabolism and Elimination — Following a single oral dose of 14 C labeled olanzapine, 7% of the dose of olanzapine was recovered in the urine as unchanged drug, indicating that olanzapine is highly metabolized. Approximately 57% and 30% of the dose was recovered in the urine and feces, respectively. In the plasma, olanzapine accounted for only 12% of the AUC for total radioactivity, indicating significant exposure to metabolites. After multiple dosing, the major circulating metabolites were the 10-N-glucuronide, present at steady state at 44% of the concentration of olanzapine, and 4'-N-desmethyl olanzapine, present at steady state at 31% of the concentration of olanzapine. Both metabolites lack pharmacological activity at the concentrations observed.

Direct glucuronidation and cytochrome P450 (CYP) mediated oxidation are the primary metabolic pathways for olanzapine. In vitro studies suggest that CYPs 1A2 and 2D6, and the flavin-containing monooxygenase system are involved in olanzapine oxidation. CYP2D6 mediated oxidation appears to be a minor metabolic pathway in vivo, because the clearance of olanzapine is not reduced in subjects who are deficient in this enzyme.

Intramuscular Formulations — There are two formulations of ZYPREXA which are available for intramuscular injection. One form (ZYPREXA RELPREV) is described in this package insert. The other formulation (ZYPREXA IntraMuscular) is a solution of olanzapine. When ZYPREXA IntraMuscular is injected intramuscularly, olanzapine (as the free base) is rapidly absorbed and peak plasma concentrations occur within 15 to 45 minutes. With the exception of higher maximum plasma concentrations, the pharmacokinetics of olanzapine after ZYPREXA IntraMuscular are similar to those for orally administered olanzapine. Refer to the package insert for ZYPREXA IntraMuscular for additional information.

Specific Populations — In general, the decision to use ZYPREXA RELPREV in specific populations should be thoughtfully considered. For patients who have never taken oral olanzapine, tolerability should be established with oral olanzapine prior to initiating treatment with ZYPREXA RELPREV. The recommended starting dose is ZYPREXA RELPREV 150 mg/4 wks, in patients who are debilitated, who have a predisposition to hypotensive reactions, who otherwise exhibit a combination of factors that may result in slower metabolism of olanzapine (e.g., nonsmoking female patients >65 years of age), or who may be more pharmacodynamically sensitive to olanzapine. When indicated, dose escalation should be performed with caution in these patients [see *Dosage and Administration* (2.1)]. Precautions noted below need to be carefully weighed.

Renal Impairment — Because olanzapine is highly metabolized before excretion and only 7% of the drug is excreted unchanged, renal dysfunction alone is unlikely to have a major impact on the pharmacokinetics of olanzapine. The pharmacokinetic characteristics of orally administered olanzapine were similar in patients with severe renal impairment and normal subjects, indicating that dosage adjustment based upon the degree of renal impairment is not required. In addition, olanzapine is not removed by dialysis. The effect of renal impairment on metabolite elimination has not been studied.

Hepatic Impairment — Although the presence of hepatic impairment may be expected to reduce the clearance of olanzapine, a study of the effect of impaired liver function in subjects (n=6) with clinically significant (Childs Pugh Classification A and B) cirrhosis revealed little effect on the pharmacokinetics of orally administered olanzapine.

Geriatric — In a study involving 24 healthy subjects, the mean elimination half-life of orally administered olanzapine was about 1.5 times greater in elderly (≥ 65 years) than in nonelderly subjects (< 65 years). Caution should be used in dosing the elderly, especially if there are other factors that might additively influence drug metabolism and/or pharmacodynamic sensitivity [see *Dosage and Administration* (2.1)].

Gender — For both oral ZYPREXA and ZYPREXA RELPREV higher average plasma concentrations of olanzapine were observed in women than in men. There were, however, no apparent differences between men and women in effectiveness or adverse effects. Dosage modifications based on gender should not be needed.

Smoking Status — For both oral ZYPREXA and ZYPREXA RELPREV, studies have demonstrated that the clearance of olanzapine is higher in smokers than in nonsmokers, although dosage modifications are not routinely recommended.

Race — In vivo studies of orally administered olanzapine have shown that exposures are similar among Japanese, Chinese and Caucasians, especially after normalization for body weight differences. Dosage modifications for race are, therefore, not recommended.

Combined Effects — The combined effects of age, smoking, and gender could lead to substantial pharmacokinetic differences in populations. The clearance in young smoking males, for example, may be 3 times higher than that in elderly nonsmoking females. Dosing modification may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of olanzapine [see *Dosage and Administration* (2.1)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis — Oral carcinogenicity studies were conducted in mice and rats. Olanzapine was administered to mice in two 78-week studies at doses of 3, 10, 30/20 mg/kg/day (equivalent to 0.8-5 times the maximum recommended human daily oral dose on a mg/m² basis) and 0.25, 2, 8 mg/kg/day (equivalent to 0.06-2 times the maximum recommended human daily oral dose on a mg/m² basis). Rats were dosed for 2 years at doses of 0.25, 1, 2.5, 4 mg/kg/day (males) and 0.25, 1, 4, 8 mg/kg/day (females) (equivalent to 0.13-2 and 0.13-4 times the maximum recommended human daily oral dose on a mg/m² basis, respectively). The incidence of liver hemangiomas and hemangiosarcomas was significantly increased in 1 mouse study in female mice dosed at 8 mg/kg/day (2 times the maximum recommended human daily oral dose on a mg/m² basis). These tumors were not increased in another mouse study in females dosed at 10 or 30/20 mg/kg/day (2-5 times the maximum recommended human daily oral dose on a mg/m² basis); in this study, there was a high incidence of early mortalities in males of the 30/20 mg/kg/day group. The incidence of mammary gland adenomas and adenocarcinomas was significantly increased in female mice dosed at ≥ 2 mg/kg/day and in female rats dosed at ≥ 4 mg/kg/day (0.5 and 2 times the maximum recommended human daily oral dose on a mg/m² basis, respectively). Rats were also treated intramuscularly with ZYPREXA RELPREV once a month for 2 years at doses of 5, 10, 20 mg/kg (males) and 10, 25, 50 mg/kg (females) (equivalent to 0.08-0.8 times the maximum recommended human dose of 300 mg every 2 weeks on a mg/m² basis; dosing was limited due to local reactions at the IM injection site). The incidence of tumors in this study was not altered when compared to solution for ZYPREXA RELPREV control or pamoic acid treated animals. Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the olanzapine carcinogenicity studies; however, measurements during subchronic toxicity studies showed that

olanzapine elevated serum prolactin levels up to 4-fold in rats at the same doses used in the carcinogenicity study. An increase in mammary gland neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin mediated. The relevance for human risk of the finding of prolactin mediated endocrine tumors in rodents is unknown [see *Warnings and Precautions* (5.17)].

Mutagenesis — No evidence of genotoxic potential for olanzapine was found in the Ames reverse mutation test, in vivo micronucleus test in mice, the chromosomal aberration test in Chinese hamster ovary cells, unscheduled DNA synthesis test in rat hepatocytes, induction of forward mutation test in mouse lymphoma cells, or in vivo sister chromatid exchange test in bone marrow of Chinese hamsters.

Impairment of Fertility — In an oral fertility and reproductive performance study in rats, male mating performance, but not fertility, was impaired at a dose of 22.4 mg/kg/day and female fertility was decreased at a dose of 3 mg/kg/day (11 and 1.5 times the maximum recommended human daily oral dose on a mg/m² basis, respectively). Discontinuance of olanzapine treatment reversed the effects on male mating performance. In female rats, the pre-coital period was increased and the mating index reduced at 5 mg/kg/day (2.5 times the maximum recommended human daily oral dose on a mg/m² basis). Diestrus was prolonged and estrus delayed at 1.1 mg/kg/day (0.6 times the maximum recommended human daily oral dose on a mg/m² basis); therefore olanzapine may produce a delay in ovulation.

13.2 Animal Toxicology and/or Pharmacology

In animal studies with olanzapine, the principal hematologic findings were reversible peripheral cytopenias in individual dogs dosed at 10 mg/kg (17 times the maximum recommended human daily oral dose on a mg/m² basis), dose-related decreases in lymphocytes and neutrophils in mice, and lymphopenia in rats. A few dogs treated with 10 mg/kg developed reversible neutropenia and/or reversible hemolytic anemia between 1 and 10 months of treatment. Dose-related decreases in lymphocytes and neutrophils were seen in mice given doses of 10 mg/kg (equal to 2 times the maximum recommended human daily oral dose on a mg/m² basis) in studies of 3 months' duration. Nonspecific lymphopenia, consistent with decreased body weight gain, occurred in rats receiving 22.5 mg/kg (11 times the maximum recommended human daily oral dose on a mg/m² basis) for 3 months or 16 mg/kg (8 times the maximum recommended human daily oral dose on a mg/m² basis) for 6 or 12 months. No evidence of bone marrow cytotoxicity was found in any of the species examined. Bone marrows were normocellular or hypercellular, indicating that the reductions in circulating blood cells were probably due to peripheral (non-marrow) factors.

14 CLINICAL STUDIES

14.1 Schizophrenia

The short-term effectiveness of ZYPREXA RELPREV was established in an 8-week, placebo-controlled trial in adult patients (n=404) who were experiencing psychotic symptoms and met DSM-IV or DSM-IV-TR criteria for schizophrenia. Patients were randomized to receive injections of ZYPREXA RELPREV 210 mg every 2 weeks, ZYPREXA RELPREV 405 mg every 4 weeks, ZYPREXA RELPREV 300 mg every 2 weeks, or placebo every 2 weeks. Patients were discontinued from their previous antipsychotics and underwent a 2-7 day washout period. No oral antipsychotic supplementation was allowed throughout the trial. The primary efficacy measure was change from baseline to endpoint in total Positive and Negative Syndrome Scale (PANSS) score (mean baseline total PANSS score 101). Total PANSS scores showed statistically significant improvement from baseline to endpoint with each dose of ZYPREXA RELPREV (210 mg every 2 weeks, 405 mg every 4 weeks, and 300 mg every 2 weeks) as compared to placebo. The effectiveness of ZYPREXA RELPREV in the treatment of schizophrenia is further supported by the established effectiveness of the oral formulation of olanzapine.

A longer-term trial enrolled patients with schizophrenia (n=1065) who had remained stable for 4 to 8 weeks on open-label treatment with oral olanzapine (mean baseline total PANSS score 56) and were then randomized to continue their current oral olanzapine dose (10, 15, or 20 mg/day); or to ZYPREXA RELPREV 150 mg every 2 weeks (405 mg every 4 weeks, 300 mg every 2 weeks, or 45 mg every 4 weeks). No oral antipsychotic supplementation was allowed throughout the trial. The primary efficacy measure was time to exacerbation of symptoms of schizophrenia defined in terms of increases in Brief Psychiatric Rating Scale (BPRS) positive symptoms or hospitalization. ZYPREXA RELPREV doses of 150 mg every 2 weeks, 405 mg every 4 weeks, and 300 mg every 2 weeks were each statistically significantly superior to low dose ZYPREXA RELPREV (45 mg every 4 weeks).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ZYPREXA RELPREV convenience kit is supplied in single-use cartons. Each carton includes one vial of olanzapine pamoate monohydrate in dosage strengths that are equivalent to 210 mg olanzapine (483 mg olanzapine pamoate monohydrate), 300 mg olanzapine (690 mg olanzapine pamoate monohydrate), and 405 mg olanzapine (931 mg olanzapine pamoate monohydrate) per vial; one vial of approximately 3 mL of diluent for ZYPREXA RELPREV used to suspend the drug product; one 3-mL syringe with pre-attached 19-gauge, 1.5-inch (38 mm) Hypodermic Needle-Pro needle with needle protection device; and two 19-gauge, 1.5-inch (38 mm) Hypodermic Needle-Pro needles with needle protection device.

Needle-Pro® is a registered trademark of Smiths Medical.
NDC 0002-7635-11 — single-use convenience kit: 210 mg vial (VL7635) with rust flip-off cap and 3-mL vial of sterile diluent (VL7622) with gray flip-off cap
NDC 0002-7636-11 — single-use convenience kit: 300 mg vial (VL7636) with olive flip-off cap and 3-mL vial of sterile diluent (VL7622) with gray flip-off cap
NDC 0002-7637-11 — single-use convenience kit: 405 mg vial (VL7637) with steel blue flip-off cap and 3-mL vial of sterile diluent (VL7622) with gray flip-off cap

16.2 Storage and Handling

ZYPREXA RELPREV should be stored at room temperature not to exceed 30°C (86°F). When the drug product is suspended in the solution for ZYPREXA RELPREV, it may be held at room temperature for 24 hours. The vial should be agitated immediately prior to product withdrawal. Once the suspension is withdrawn into the syringe, it should be used immediately [see *Dosage and Administration* (2.2)].

17 PATIENT COUNSELING INFORMATION

See *FDA-approved Medication Guide*.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking ZYPREXA RELPREV. Patients should be advised to call their doctor if they do not think they are getting better or have concerns about their condition.

17.1 Information on Medication Guide

Prescribers or other health professionals should inform patients, their families, and their caregivers about the potential benefits and potential risks associated with treatment with ZYPREXA RELPREV, and should counsel them in its appropriate use. A patient Medication Guide is available for ZYPREXA RELPREV. Prescribers or other health professionals should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have.

17.2 Post-Injection Delirium/Sedation Syndrome

During premarketing clinical studies, reactions that presented with signs and symptoms consistent with olanzapine overdose have been reported in patients following an injection of ZYPREXA RELPREVV. It is mandatory that patients be enrolled in the ZYPREXA RELPREVV Patient Care Program to receive ZYPREXA RELPREVV treatment. Patients should be advised of the risk of post-injection delirium/sedation syndrome each time they receive an injection [see *Warnings and Precautions* (5.1, 5.2)]. Patient and caregivers should be advised that after each ZYPREXA RELPREVV injection, patients must be observed at the healthcare facility for at least 3 hours and must be accompanied to their destination upon leaving the facility. The Medication Guide should be distributed each time patients receive an injection.

17.3 Elderly Patients with Dementia-Related Psychosis: Increased Mortality and Cerebrovascular Adverse Events (CVAE), Including Stroke

Patients and caregivers should be advised that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Patients and caregivers should be advised that elderly patients with dementia-related psychosis treated with ZYPREXA had a significantly higher incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) compared with placebo.

ZYPREXA RELPREVV is not approved for elderly patients with dementia-related psychosis [see *Boxed Warning and Warnings and Precautions* (5.3)].

17.4 Neuroleptic Malignant Syndrome (NMS)

Patients and caregivers should be counseled that a potentially fatal symptom complex sometimes referred to as NMS has been reported in association with administration of antipsychotic drugs, including ZYPREXA. Signs and symptoms of NMS include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia) [see *Warnings and Precautions* (5.5)].

17.5 Hyperglycemia

Patients should be advised of the potential risk of hyperglycemia-related adverse reactions related to ZYPREXA RELPREVV. Patients should be monitored regularly for worsening of glucose control. Patients who have diabetes should follow their doctor's instructions about how often to check their blood sugar while taking ZYPREXA RELPREVV [see *Warnings and Precautions* (5.6)].

17.6 Hyperlipidemia

Patients should be counseled that hyperlipidemia has occurred during treatment with ZYPREXA RELPREVV. Patients should have their lipid profile monitored regularly [see *Warnings and Precautions* (5.7)].

17.7 Weight Gain

Patients should be counseled that weight gain has occurred during treatment with ZYPREXA RELPREVV. Patients should have their weight monitored regularly [see *Warnings and Precautions* (5.8)].

17.8 Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension, and in association with the use of concomitant drugs that may potentiate the orthostatic effect of ZYPREXA RELPREVV, e.g., diazepam or alcohol [see *Warnings and Precautions* (5.10) and *Drug Interactions* (7)]. Patients should be advised to change positions carefully to help prevent orthostatic hypotension, and to lie down if they feel dizzy or faint, until they feel better. Patients should be advised to call their doctor if they experience any of the following signs and symptoms associated with orthostatic hypotension: dizziness, fast or slow heart beat, or fainting.

17.9 Potential for Cognitive and Motor Impairment

Because ZYPREXA RELPREVV has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that ZYPREXA RELPREVV therapy does not affect them adversely. Additionally, due to the risk of post-injection delirium/sedation syndrome, patients should not drive or operate heavy machinery for the remainder of the day of each injection [see *Dosage and Administration* (2.1) and *Warnings and Precautions* (5.1, 5.14)].

17.10 Body Temperature Regulation

Patients should be advised regarding appropriate care in avoiding overheating and dehydration. Patients should be advised to call their doctor right away if they become severely ill and have some or all of these symptoms of dehydration: sweating too much or not at all, dry mouth, feeling very hot, feeling thirsty, not able to produce urine [see *Warnings and Precautions* (5.15)].

17.11 Concomitant Medication

Patients should be advised to inform their physicians if they are taking, or plan to take, ZYPREXA or Symbyax® (olanzapine/fluoxetine combination). Patients should also be advised to inform their physicians if they are taking, plan to take, or have stopped taking any prescription or over-the-counter drugs, including herbal supplements, since there is a potential for interactions [see *Drug Interactions* (7)].

17.12 Alcohol

Patients should be advised to avoid alcohol while taking ZYPREXA RELPREVV [see *Drug Interactions* (7.1)].

17.13 Use in Specific Populations

Pregnancy — Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with ZYPREXA RELPREVV [see *Use in Specific Populations* (8.1)].

Nursing Mothers — Patients should be advised not to breast-feed an infant if they are taking ZYPREXA RELPREVV [see *Use in Specific Populations* (8.3)].

Pediatric Use — Safety and effectiveness of ZYPREXA RELPREVV in patients under 18 years have not been established [see *Use in Specific Populations* (8.4)].

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PV 5924 AMP

ZYPREXA RELPREVV (olanzapine) For Extended Release Injectable Suspension

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ZYPREXA RELPREVV (olanzapine) For Extended Release Injectable Suspension

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Medication Guide

ZYPREXA® RELPREVV™ (zy-PREX-a REL-prev)

(olanzapine)

For Extended Release Injectable Suspension

Read the Medication Guide that comes with ZYPREXA RELPREVV before you start taking it and each time before you get an injection. There may be new information. This Medication Guide does not take the place of talking to your doctor about your medical condition or treatment. Talk with your doctor if there is something you do not understand or you want to learn more about ZYPREXA RELPREVV.

What is the most important information I should know about ZYPREXA RELPREVV?

Before you receive ZYPREXA RELPREVV treatment you must:

- **understand the risks and benefits of ZYPREXA RELPREVV treatment. Your doctor will talk to you about the risks and benefits of ZYPREXA RELPREVV treatment.**
- **register in the ZYPREXA RELPREVV Patient Care Program. You must agree to the rules of the ZYPREXA RELPREVV Patient Care Program before you register.**

ZYPREXA RELPREVV may cause serious side effects, including:

1. **Post-injection Delirium Sedation Syndrome (PDSS).**
2. **Increased risk of death in elderly people who are confused, have memory loss and have lost touch with reality (dementia-related psychosis).**
3. **High blood sugar (hyperglycemia).**
4. **High fat levels in your blood (increased cholesterol and triglycerides), especially in teenagers age 13 to 17.**
5. **Weight gain, especially in teenagers age 13 to 17.**

These serious side effects are described below.

1. **Post-injection Delirium Sedation Syndrome (PDSS).** PDSS is a serious problem that can happen after you get a ZYPREXA RELPREVV injection if the medicine gets in your blood too fast. This problem usually happens within 3 hours after you receive ZYPREXA RELPREVV. If the medicine gets in your blood too fast, you may have some of the following symptoms:
 - feel more sleepy than usual
 - feel dizzy
 - feel confused or disoriented
 - trouble talking or walking
 - muscles feel stiff or shaking
 - feel weak
 - feel grouchy or angry
 - feel nervous or anxious
 - higher blood pressure
 - seizures (convulsions)
 - pass out (become unconscious or coma)

You will need to stay at the clinic where you receive the injection for at least 3 hours so your doctor can make sure you do not have symptoms of PDSS. When you leave the clinic someone must be with you. If you have symptoms of PDSS after you leave the clinic, get medical help or go to an emergency room right away.

2. **Increased risk of death in elderly people who are confused, have memory loss and have lost touch with reality (dementia-related psychosis).** ZYPREXA RELPREVV is not approved for treating psychosis in elderly people with dementia.
3. **High blood sugar (hyperglycemia).** High blood sugar can happen if you have diabetes already or if you have never had diabetes. High blood sugar could lead to:

- a build up of acid in your blood due to ketones (ketoacidosis)
- coma
- death

Your doctor should do tests to check your blood sugar before you start taking ZYPREXA RELPREVV and during treatment. In people who do not have diabetes, sometimes high blood sugar goes away when ZYPREXA RELPREVV is stopped. People with diabetes and some people who did not have diabetes before taking ZYPREXA RELPREVV need to take medicine for high blood sugar even after they stop taking ZYPREXA RELPREVV.

If you have diabetes, follow your doctor's instructions about how often to check your blood sugar while taking ZYPREXA RELPREVV.

Call your doctor if you have any of these symptoms of high blood sugar (hyperglycemia) while taking ZYPREXA RELPREVV:

- feel very thirsty
- need to urinate more than usual
- feel very hungry
- feel weak or tired
- feel sick to your stomach
- feel confused or your breath smells fruity

4. **High fat levels in your blood (cholesterol and triglycerides).** High fat levels may happen in people treated with ZYPREXA RELPREVV, especially in teenagers (13 to 17 years old). ZYPREXA RELPREVV is not approved in patients less than 18 years old. You may not have any symptoms, so your doctor should do blood tests to check your cholesterol and triglyceride levels before you start taking ZYPREXA RELPREVV and during treatment.

5. **Weight gain.** Weight gain is very common in people who take ZYPREXA RELPREVV. Teenagers (13 to 17 years old) are more likely to gain weight and to gain more weight than adults. ZYPREXA RELPREVV is not approved in patients less than 18 years old. Some people may gain a lot of weight while taking ZYPREXA RELPREVV, so you and your doctor should check your weight regularly. Talk to your doctor about ways to control weight gain, such as eating a healthy, balanced diet, and exercising.

What is ZYPREXA RELPREVV?

ZYPREXA RELPREVV is a long-acting prescription medicine given by injection and used to treat schizophrenia in adults. The symptoms of schizophrenia include:

- hearing voices
- seeing things that are not there
- having beliefs that are not true
- being suspicious or withdrawn

Some of your symptoms of schizophrenia may improve with treatment with ZYPREXA RELPREVV. If you do not think you are getting better, call your doctor.

It is not known if ZYPREXA RELPREVV is safe and effective in children under 18 years of age.

What should I tell my doctor before taking ZYPREXA RELPREVV?

ZYPREXA RELPREVV may not be right for you. Before starting ZYPREXA RELPREVV, tell your doctor if you have or had:

- heart problems
- seizures
- diabetes or high blood sugar levels (hyperglycemia)
- high cholesterol or triglyceride levels in your blood
- liver problems
- low or high blood pressure
- strokes or "mini-strokes" also called transient ischemic attacks (TIAs)
- Alzheimer's disease
- narrow-angle glaucoma
- enlarged prostate in men
- bowel obstruction
- breast cancer

- thoughts of suicide or hurting yourself
- any other medical condition
- are pregnant or plan to become pregnant. It is not known if ZYPREXA RELPREVV will harm your unborn baby.
- are breast-feeding or plan to breast-feed. ZYPREXA RELPREVV can pass into your breast milk and may harm your baby. You should not breast-feed while taking ZYPREXA RELPREVV. Talk to your doctor about the best way to feed your baby if you take ZYPREXA RELPREVV.

Tell your doctor if you exercise a lot or are in hot places often.

The symptoms of schizophrenia may include **thoughts of suicide** or of hurting yourself or others. If you have these thoughts at any time, tell your doctor or go to an emergency room right away.

Tell your doctor about all the medicines that you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. ZYPREXA RELPREVV and some medicines may interact with each other and may not work as well, or cause possible serious side effects. Your doctor can tell you if it is safe to take ZYPREXA RELPREVV with your other medicines. Do not start or stop any medicine while taking ZYPREXA RELPREVV without talking to your doctor first.

How should I receive ZYPREXA RELPREVV?

- ZYPREXA RELPREVV will be injected into the muscle in your buttock (gluteus) by your doctor or nurse at the clinic.
- After receiving ZYPREXA RELPREVV, you will need to stay at the clinic for at least 3 hours.
- When you leave the clinic, someone must be with you.
- Call your doctor if you do not think you are getting better or have any concerns about your condition while taking ZYPREXA RELPREVV.

What should I avoid while receiving ZYPREXA RELPREVV?

- ZYPREXA RELPREVV can cause sleepiness and may affect your ability to make decisions, think clearly, or react quickly. Do not drive, operate heavy machinery, or do other dangerous activities until you know how ZYPREXA RELPREVV affects you. You should not drive or operate heavy machinery for the rest of the day after each injection.
- Avoid drinking alcohol while taking ZYPREXA RELPREVV. Drinking alcohol while you take ZYPREXA RELPREVV may make you sleepier than if you take ZYPREXA RELPREVV alone.

What are the possible side effects of ZYPREXA RELPREVV?

Serious side effects may happen when you take ZYPREXA RELPREVV, including:

- See “What is the most important information I should know about ZYPREXA RELPREVV?”, which describes the risk of **post-injection delirium sedation syndrome (PDSS)**, increased risk of death in elderly people with dementia-related psychosis and the risks of high blood sugar, high cholesterol and triglyceride levels, and weight gain.
- **Increased incidence of stroke or “mini-strokes” called transient ischemic attacks (TIAs) in elderly people with dementia-related psychosis** (elderly people who have lost touch with reality due to confusion and memory loss). ZYPREXA RELPREVV is not approved for these patients.
- **Neuroleptic Malignant Syndrome (NMS):** NMS is a rare but very serious condition that can happen in people who take antipsychotic medicines, including ZYPREXA RELPREVV. NMS can cause death and must be treated in a hospital. Call your doctor right away if you become severely ill and have any of these symptoms:
 - high fever
 - excessive sweating
 - rigid muscles
 - confusion
 - changes in your breathing, heartbeat, and blood pressure
- **Tardive Dyskinesia:** This condition causes body movements that keep happening and that you can not control. These movements usually affect the face and tongue. Tardive dyskinesia may not go away, even if you stop

taking ZYPREXA RELPREVV. It may also start after you stop taking ZYPREXA RELPREVV. Tell your doctor if you get any body movements that you can not control.

- **Decreased blood pressure when you change positions, with symptoms of dizziness, fast or slow heartbeat, or fainting.**
- **Difficulty swallowing, that can cause food or liquid to get into your lungs.**
- **Seizures: Tell your doctor if you have a seizure during treatment with ZYPREXA RELPREVV.**
- **Problems with control of body temperature:** You could become very hot, for instance when you exercise a lot or stay in an area that is very hot. It is important for you to drink water to avoid dehydration. Call your doctor right away if you become severely ill and have any of these symptoms of dehydration:
 - sweating too much or not at all
 - dry mouth
 - feeling very hot
 - feeling thirsty
 - not able to produce urine

Common side effects of ZYPREXA RELPREVV include: headache, sleepiness or drowsiness, weight gain, dry mouth, diarrhea, nausea, common cold, eating more (increased appetite), vomiting, cough, back pain, or pain at the injection site.

Tell your doctor about any side effect that bothers you or that does not go away.

These are not all the possible side effects with ZYPREXA RELPREVV. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about ZYPREXA RELPREVV

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.

This Medication Guide summarizes the most important information about ZYPREXA RELPREVV. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about ZYPREXA RELPREVV that was written for healthcare professionals. For more information about ZYPREXA RELPREVV call 1-800-Lilly-Rx (1-800-545-5979) or visit www.zyprexarelpbev.com.

What are the ingredients in ZYPREXA RELPREVV?

Active ingredient: olanzapine

Inactive ingredients: carboxymethylcellulose sodium, mannitol, polysorbate 80, sodium hydroxide and/or hydrochloric acid for pH adjustment, and water for injection

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Medication Guide revised August 3, 2012

Lilly

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Indianapolis, IN 46285, USA

www.zyprexarelpbev.com

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PV 5942 AMP

ZYPREXA RELPREVV (olanzapine) For Extended Release Injectable Suspension

PV 5942 AMP

ZYPREXA RELPREVV (olanzapine) For Extended Release Injectable Suspension

PV 5942 AMP

CHAPTER 1: INTRODUCTION		
1	Title: ZYPREXA RELPREVV Reconstitution and Administration Training Video CHAPTER ONE: INTRODUCTION	
2	Text on-screen: ZYPREXA RELPREVV (olanzapine) For Extended Release Injectable Suspension is an antipsychotic agent indicated for treatment of schizophrenia in adults.	
3	Text on-Screen: All healthcare professionals who administer this product must view this video before giving an injection of ZYPREXA RELPREVV. For important safety Information, including boxed warnings, see the end of this program and the full prescribing information provided.	Narrator: All healthcare professionals who administer this product must view this video before giving an injection of ZYPREXA RELPREVV
4	Fade up to video of nurse (talent) talking to camera. Text on-Screen: Vial strengths 210 mg, 300 mg, and 405 mg Dosing schedules Every 2 weeks: 150-mg, 210-mg, or 300-mg doses Every 4 weeks: 300-mg or 405-mg doses	Narrator: ZYPREXA RELPREVV is a long acting injectable formulation of olanzapine. It is indicated for treatment of schizophrenia in adults. The efficacy of ZYPREXA RELPREVV is consistent with the established efficacy of orally administered Zyprexa for treatment of schizophrenia in adults. ZYPREXA RELPREVV is available in 210-, 300-, and 405-milligram vials. It may be administered every 2 weeks in 150-mg, 210-mg, or 300-mg doses, or every 4 weeks in 300-mg or 405-mg doses.
5	Text on-Screen: <ul style="list-style-type: none"> • Description of Post-Injection Delirium/ Sedation Syndrome • Demonstration of ZYPREXA RELPREVV product reconstitution • Demonstration of 	Narrator: The purpose of this video is to teach you how to properly reconstitute and administer ZYPREXA RELPREVV. First we will begin by explaining the Post-Injection Delirium/Sedation Syndrome events that occurred with ZYPREXA RELPREVV in pre-marketing clinical trials. Then, we will demonstrate step-by-step instructions on how to properly reconstitute the product. Once it has been

	<p>injection technique</p> <ul style="list-style-type: none"> • Real-time demonstration of reconstitution and administration process 	<p>reconstituted, we will show you the proper administration techniques and demonstrate the entire reconstitution and administration process in real time.</p> <p>Please watch the end of this video and see accompanying full prescribing information for important safety information including boxed warnings.</p>
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CHAPTER 2: POST-INJECTION DELIRIUM/SEDATION SYNDROME

6	<p>Text on screen: CHAPTER TWO: POST-INJECTION DELIRIUM/ SEDATION SYNDROME</p> <p>Events occurred: in <0.1% of injections in approximately 2% of patients</p> <p>Symptoms: Sedation: ranging from mild in severity up to coma Delirium: confusion, disorientation, agitation, anxiety and other cognitive impairment.</p> <p>Other Symptoms: extrapyramidal symptoms, dysarthria, ataxia, aggression, dizziness, weakness, hypertension, possible convulsion.</p> <p>PDSS</p> <table border="1" data-bbox="284 1381 649 1543"> <thead> <tr> <th>Time of Onset of Symptoms</th> <th>Patients</th> </tr> </thead> <tbody> <tr> <td><60 minutes</td> <td>~80%</td> </tr> <tr> <td>1 to 3 hours</td> <td>~ 14%</td> </tr> <tr> <td>>3 hours</td> <td>~ 6%</td> </tr> </tbody> </table> <p>Observe patients for 3 hours for symptoms of PDSS If parenteral benzodiazepines are required for patient management during a PDSS event, careful evaluation of clinical status for excessive</p>	Time of Onset of Symptoms	Patients	<60 minutes	~80%	1 to 3 hours	~ 14%	>3 hours	~ 6%	<p>Narrator: During pre-marketing clinical studies, events that presented with signs and symptoms consistent with olanzapine overdose were reported in some patients following an injection of ZYPREXA RELPREVV. These events occurred in <0.1% of injections and in approximately 2% of patients who received injections for up to 46 months.</p> <p>Most of these patients developed symptoms of sedation, ranging from mild in severity up to coma, and/or delirium, including confusion, disorientation, agitation, anxiety and other cognitive impairment. Other symptoms noted include extrapyramidal symptoms, dysarthria, ataxia, aggression, dizziness, weakness, hypertension or possible convulsion.</p> <p>In pre-marketing clinical trials, the potential for onset of a PDSS event was greatest within the first hour. The majority of cases have occurred within the first 3 hours after injection; however the event has occurred after 3 hours. Patients should be advised of this potential risk and the need to be observed for 3 hours in a healthcare facility each time ZYPREXA RELPREVV is administered.</p> <p>Patients experiencing post-injection delirium/sedation syndrome should be managed as clinically appropriate. Patients may be treated symptomatically.</p> <p>If a Post-injection Delirium/Sedation Syndrome event is suspected, close medical supervision and monitoring should be conducted in a facility capable of resuscitation.</p>
Time of Onset of Symptoms	Patients									
<60 minutes	~80%									
1 to 3 hours	~ 14%									
>3 hours	~ 6%									

	<p>sedation and cardiorespiratory depression is recommended.</p> <p>Notify hospital or ER personnel of: “...a probable olanzapine overdose following administration of Olanzapine For Extended Release Injectable Suspension.”</p> <p>IMPORTANT: Before administering the injection, confirm there will be someone to accompany the patient after the 3-hour observation period. If this cannot be confirmed, do not give the injection.</p>	<p>If parenteral benzodiazepines are required for patient management during a PDSS event, careful evaluation of clinical status for excessive sedation and cardiorespiratory depression is recommended.</p> <p>If the patient is sent to a hospital or ER for further observation or management, notify the hospital or ER personnel that the patient is experiencing “a probable olanzapine overdose following administration of Olanzapine For Extended Release Injectable Suspension.”</p> <p>An important reminder: before administering the injection, confirm there will be someone to accompany the patient after the 3-hour observation period. If this cannot be confirmed, do not give the injection.</p>
7	<p>Text on-Screen: After each injection:</p> <ul style="list-style-type: none"> • Patients should be observed for at least 3 hours by appropriately qualified personnel in a healthcare facility with ready access to emergency response services • The patient should be located where he or she can be seen and/or heard at all times 	<p>Narrator: After each ZYPREXA RELPREVV injection:</p> <ul style="list-style-type: none"> • Patients should be observed for at least 3 hours by appropriately qualified personnel in a healthcare facility with ready access to emergency response services • The patient should be located where he or she can be seen and/or heard at all times
8	<p>Text on-Screen: Before patient leaves the healthcare facility:</p> <ul style="list-style-type: none"> • Confirm that the patient is alert, oriented, and without signs or symptoms of a post-injection delirium/sedation syndrome event 	<p>Narrator: Before the patient leaves the healthcare facility:</p> <ul style="list-style-type: none"> • Confirm that the patient is alert, oriented, and without signs or symptoms of a post-injection syndrome event • Advise patients and their caregivers to be vigilant for symptoms of a post-injection syndrome event for the remainder of the day and be able to obtain assistance if needed • All patients should be accompanied to their next

	<ul style="list-style-type: none"> • Advise patients and their caregivers to be vigilant for symptoms of a post -injection delirium/sedation syndrome event for the remainder of the day and be able to obtain assistance if needed • All patients should be accompanied to their next destination upon leaving the facility 	<p>destination upon leaving the facility</p>
9	<p>Text on-Screen: After patient leaves the healthcare facility:</p> <ul style="list-style-type: none"> • Patients should not drive or operate heavy machinery for remainder of day 	<p>Narrator: After leaving the healthcare facility:</p> <ul style="list-style-type: none"> ➤ Patients should not drive or operate heavy machinery for the remainder of day <p>In addition, patient ID cards and wristbands are available for distribution to patients who receive ZYPREXA RELPREVV. The patient ID cards can be used to record the date and time of injection, concomitant medications, and emergency contact information. The wristbands can be used to note the date of the injection and an emergency contact number. Please contact your Lilly sales representative to receive a supply of patient ID cards and wristbands to use in your treatment facility.</p>
10	<p>Text on-Screen: Increased contact with blood can occur:</p> <ul style="list-style-type: none"> ➤ Partial injection into vasculature ➤ Significant vessel injury during IM injection (nick or puncture) ➤ Substantial bleeding at injection site 	<p>Narrator: ZYPREXA RELPREVV is much more soluble in blood than in muscle. Increased contact with a substantial volume of blood could occur in several ways, such as</p> <ul style="list-style-type: none"> ➤ Partial injection into vasculature ➤ Vessel injury associated with the intramuscular injection (a nick or puncture of the blood vessel) ➤ And substantial bleeding at injection site

	<p>Text on-screen: Deep intramuscular gluteal injection:</p> <ul style="list-style-type: none"> • Intended for deep muscular gluteal injection only <ul style="list-style-type: none"> ○ Not for intravenous, subcutaneous, or deltoid injection • Aspirate syringe prior to injection to ensure no blood is visible • If blood is visible, discard the syringe and use a new product kit 	<p>Therefore, ZYPREXA RELPREVV is intended for deep intramuscular gluteal injection only. It is important to aspirate the syringe prior to injection to ensure no blood is visible. Administrators must not proceed with the injection if blood is visible. If blood is visible, discard the syringe and use a new product kit.</p>
	<p>Text on-screen:</p> <ul style="list-style-type: none"> • Post-Injection Delirium/Sedation Syndrome can occur at any injection 	<p>Post-injection Delirium/Sedation Syndrome can occur at any injection, so safety precautions should be observed every time the product is administered.</p>
CHAPTER 3: PREPARE MATERIALS		
11	<p>Text on-screen: CHAPTER THREE: STEP 1- Prepare Materials</p> <p>Pair of hands placing gloves and alcohol wipes on counter.</p> <p>Arrange materials on counter.</p> <p>Close-up of contents of kit.</p> <p>Put gloves on hands.</p>	<p>Narrator: Let's begin by preparing for the ZYPREXA RELPREVV injection.</p> <p>First, you will need to gather and prepare your materials.</p> <p>Obtain 1 pair of gloves, several alcohol wipes, and the prescribed dose of ZYPREXA RELPREVV. The medication comes packaged in a convenience kit that includes the following items: A vial of ZYPREXA RELPREVV powder; a 3ml vial of diluent, one Needle-Pro® 3ml syringe with attached 19 gauge, 1.5 inch safety needle, 2 additional 19-gauge, 1.5 inch safety needles, a Reconstitution and Administration leaflet, and a patient Medication Guide.</p> <p>Open the kit, remove all items, and arrange them conveniently to prepare for reconstitution.</p> <p>You will need to wear gloves when reconstituting</p>

		ZYPREXA RELPREVV, as the medication can be irritating to the skin. If the medication contacts skin, flush it with water.
CHAPTER 4: DETERMINE RECONSTITUTION VOLUME		
12	<p>Text on-screen: CHAPTER FOUR: STEP 2: DETERMINE RECONSTITUTION VOLUME</p> <p>Close-up of table...</p> <p>Text on-screen: There will be excess diluent remaining in the vial.</p>	<p>Narrator: Next you will need to determine the reconstitution volume. Please refer to the table in the full-color reconstitution and administration instructions for the proper volumes of diluent to add for each vial strength.</p> <p>For example, if you are preparing a 210mg dose, you will need to add 1.3ml of diluent to the 210mg powder vial.</p> <p>It is important to note that no matter what dose you are preparing, there will be excess diluent remaining in the vial. This extra diluent will not be needed.</p>
CHAPTER 5: RECONSTITUTE		
13	<p>Text on-screen: CHAPTER FIVE: RECONSTITUTE</p> <p>Tap the vial.</p> <p>Withdraw 1.3ml of diluent.</p> <p>Inject diluent into vial. While needle is still in vial, pull back on the plunger.</p> <p>Hold vial upright when removing needle</p> <p>Engage safety syringe.</p> <p>Tap vial on hard surface. Text on screen: Tap firmly and repeatedly</p>	<p>Narrator: Now you are ready to reconstitute ZYPREXA RELPREVV. The process of reconstitution and administration should take around 5 minutes to complete.</p> <p>First, loosen the powder by lightly tapping the vial a few times. The powder should be free flowing. This step helps to ensure the powder suspends easily and thoroughly after the diluent is added.</p> <p>Withdraw the proper amount of diluent into the syringe. In this case, the vial strength is 210mg, so we will withdraw 1.3ml of solution.</p> <p>Inject the diluent into the powder vial. Before you withdraw the needle, pull back on the plunger to withdraw some air. This will help equalize pressure in the vial.</p> <p>Hold the vial upright when removing the needle to prevent any loss of medication.</p> <p>Next, engage the safety needle and push the air out of the syringe.</p> <p>The suspension must be mixed correctly to ensure proper dosing. Tap the vial firmly and repeatedly on a hard, cushioned surface until there is no powder</p>

	<p>Close-up of vial, looking for clumps. Tap vial again, if clumps are seen.</p> <p>Shake vial vigorously. Close-up of suspension.</p> <p>Foam in vial. Set vial on hard surface for foam to dissipate.</p> <p>Text on-screen: Product is stable in the vial for 24 hours after reconstitution.</p>	<p>visible. Avoid shaking the vial before tapping, as this can make it more difficult to suspend.</p> <p>Check for clumps by inspecting the sides and bottom of the vial. Unsuspended powder appears as light yellow, dry clumps clinging to the vial. If clumps are visible, tap the vial again to break the clumps free.</p> <p>Shake the vial vigorously until the suspension appears smooth and consistent in color and texture.</p> <p>Sometimes foam will form from shaking the vial. The foam will dissipate if you let the vial stand briefly. You should avoid drawing foam up into the syringe, as the excess air bubbles are hard to remove and may affect the accuracy of the dose.</p> <p>Once reconstituted, the suspension is stable in the vial for up to 24 hours and does not require refrigeration. However, if the suspension is not used immediately, it should be shaken to resuspend before being drawn into the syringe for administration. Once drawn up into the syringe, this medication should be injected immediately.</p>
CHAPTER 6: INJECT ZYPREXA RELPREVV		
14	<p>Text on-Screen: CHAPTER SIX: INJECT ZYPREXA RELPREVV</p> <p>Close-up of table in instructions.</p> <p>1.4ml withdrawn from vial.</p> <p>Text on-screen: There will be excess medication remaining in the vial.</p> <p>Tap the syringe.</p>	<p>Narrator: Attach a new safety needle to the syringe.</p> <p>For all doses, the concentration of olanzapine in the suspension is 150 mg per 1 ml.</p> <p>When preparing to draw up the prescribed dose, refer to the table in the instructions for the correct injection volume.</p> <p>For a prescribed dose of 210mg, you will withdraw 1.4ml from the reconstituted vial. To prevent the product from leaking from the stopper, do not add air to the vial. Slowly withdraw the desired amount into the syringe. By doing this slowly, you will avoid excess air bubbles being drawn into the syringe. There will be excess medication remaining in the vial.</p> <p>To ensure the full dose is given, tap the syringe with your fingers to remove all excess air bubbles.</p> <p>Once the desired dose is withdrawn, remove the needle from the vial, and engage the needle safety</p>

	Engage needle safety device. Safety needle attached to syringe.	device. Attach a new safety needle to the syringe.
15	Text on-screen: Important: Prior to administration, you must make sure that the patient receiving ZYPREXA RELPREVV will be accompanied to his or her destination following the 3-hour observation period. If this cannot be confirmed, do not give the injection. Text on-screen: Important: The patient may not drive to his or her destination for the rest of the day. Text On-Screen: Do not inject the medication intravenously or subcutaneously. Graphic/Model showing ventrogluteal and dorsogluteal muscles.	Narrator: Prior to administration, you must make sure that the patient receiving ZYPREXA RELPREVV will be accompanied to his or her destination following the 3-hour observation period. If this cannot be confirmed, do not give the injection. Even if accompanied, the patient may not drive to his or her destination or for the rest of the day of injection. Now you are ready to give the injection of ZYPREXA RELPREVV. Once the medication is drawn into the syringe, it should be injected immediately. First, select and prepare a site for injection. This injection can be given in the ventrogluteal or the dorsogluteal muscle. These two areas have large muscle density and are clinically appropriate sites for deep gluteal injections. For these demonstrations, we are using an anatomical model. The model is not designed to receive product, so we will be using an empty syringe to show the injection should be administered.
CHAPTER 7: VENTROGLUTEAL INJECTION		
16	Text on-screen: CHAPTER SEVEN: VENTROGLUTEAL INJECTION Insert needle into correct location on model. Pull back on plunger. Withdraw needle from model, engage safety device.	Narrator: To give a ventrogluteal injection, place the heel of your hand on the greater trochanter, or hip bone at the top of the thigh. Your wrist will be in line with the person's thigh. Point your thumb at the groin and fingers towards the person's head. Form a "V" by opening a space between your pointer finger and the other three fingers. The place to give the injection is in the middle of the V-shaped triangle.

	Dispose of vials, syringe safely.	<p>Insert the needle into the muscle, then aspirate slowly for several seconds by pulling back on the plunger of the syringe. If any blood is drawn into the syringe, discard the syringe and the dose, and begin with a new kit.</p> <p>In this case, no blood is seen, so we will inject the medication with steady pressure.</p> <p>After withdrawing the needle carefully from the muscle, engage the needle safety device.</p> <p>Do not massage the injection site.</p> <p>Finally, after the injection, make sure to dispose of the vials, needles, and syringe appropriately.</p>
CHAPTER 8: DORSOGLUTEAL INJECTION		
17	<p>Text on-screen: CHAPTER EIGHT: DORSOGLUTEAL INJECTION</p> <p>Insert needle into correct location on model. Pull back on plunger.</p> <p>Withdraw needle from model, engage safety device.</p> <p>Text On-Screen: Do not massage the area after the injection.</p> <p>Dispose of vials, syringe safely.</p> <p>Text On-Screen: Note: The vial is for single use only.</p>	<p>Narrator: To administer a dorsogluteal injection, first locate the upper quadrant of the buttocks by drawing an imaginary line across and down, dividing the buttocks into 4 quadrants.</p> <p>Insert the needle into the gluteal muscle, then aspirate slowly for several seconds by pulling back on the plunger of the syringe. If any blood is drawn into the syringe, discard the syringe and the dose, and begin with a new kit.</p> <p>In this case, no blood is seen, so we will inject the medication with a steady pressure.</p> <p>After withdrawing the needle carefully from the gluteal muscle, engage the needle safety device.</p> <p>Do not massage the injection site.</p> <p>Finally, after the injection, make sure to dispose of the vials, needles, and syringe appropriately.</p>
CHAPTER 9: RECAP		
18	<p>Text on Screen: CHAPTER NINE: RECAP</p> <ul style="list-style-type: none"> • Prepare Materials • Determine Reconstitution Volume 	<p>Narrator: To summarize, the process of reconstituting and administering ZYPREXA RELPREVV can be broken down into four easy steps, One: Prepare Materials. Two: Determine Reconstitution Volume. Three: Reconstitute; and four, Inject.</p>

	<ul style="list-style-type: none"> • Reconstitute • Inject 	
19	Go through process of reconstitution in real-time. Provide Stop Watch to be shown on-screen.	Narrator: Watch as we demonstrate the entire process in real time. Remember, for these demonstrations, we are using an anatomical model. The model is not designed to receive product, so we will be using an empty syringe to show how the injection should be administered.
20	Text on Screen: 1-800-LillyRx (1-800-545-5979) www.ZyprexaRelprevv.com	Narrator: If you have any questions about reconstituting and administering ZYPREXA RELPREVV please contact the number on-screen or visit the following website.
CHAPTER 10: IMPORTANT SAFETY INFORMATION (scrolled no voice-over)		
21	Text on-screen: Current ISI will scroll at the end of the video	

Instructions to Reconstitute and Administer ZYPREXA RELPREVV



ZYPREXA Relprevv™
(olanzapine) For Extended Release
Injectable Suspension

FOR DEEP INTRAMUSCULAR GLUTEAL INJECTION ONLY.
NOT TO BE INJECTED INTRAVENOUSLY OR SUBCUTANEOUSLY.

For Important Safety Information, including boxed warnings, see the full Prescribing Information provided.

STEP 1 PREPARING MATERIALS



Figure 1: Contents of convenience kit.

Convenience kit includes:

(See Figure 1 on left)

- Vial of ZYPREXA RELPREVV powder
- 3-mL vial of diluent
- One 3-mL syringe with pre-attached 19-gauge, 1.5-inch (38 mm) Hypodermic Needle-Pro® needle with needle protection device
- Two 19-gauge, 1.5-inch (38 mm) Hypodermic Needle-Pro needles with needle protection device.
 - For obese patients, a 2-inch (50 mm), 19-gauge or larger needle (not included in convenience kit) may be used for administration.

! ZYPREXA RELPREVV must be suspended using only the diluent supplied in the convenience kit.

It is recommended that gloves are used when reconstituting, as ZYPREXA RELPREVV may be irritating to the skin. Flush with water if contact is made with skin.

STEP 2 DETERMINING RECONSTITUTION VOLUME

Dose	Vial Strength	Diluent to Add
150 mg	210 mg	1.3 mL
210 mg	210 mg	1.3 mL
300 mg	300 mg	1.8 mL
405 mg	405 mg	2.3 mL

Refer to the table at left to determine the amount of diluent to be added to powder for reconstitution of each vial strength.

! It is important to note that there is more diluent in the vial than is needed to reconstitute.

STEP 3 RECONSTITUTING ZYPREXA RELPREVV



Figure 2: Tap firmly to mix.



Figure 3: Check for unsuspended powder and repeat tapping if needed.



Figure 4: Vigorously shake vial.

- Loosen the powder by lightly tapping the vial.
- Open the prepackaged Hypodermic Needle-Pro syringe and needle with needle protection device.
- Withdraw the pre-determined diluent volume (Step 2) into the syringe.
- Inject the diluent into the powder vial.
- Withdraw air to equalize the pressure in the vial by pulling back slightly on the plunger in the syringe.
- Remove the needle from the vial, holding the vial upright to prevent any loss of material.
- Engage the needle safety device (refer to complete Hypodermic Needle-Pro instruction for use).
- Pad a hard surface to cushion impact (see Figure 2). Tap the vial firmly and repeatedly on the surface until no powder is visible.
- Visually check the vial for clumps. Unsuspended powder appears as yellow, dry clumps clinging to the vial. Additional tapping may be required if large clumps remain (see Figure 3).
- Shake the vial vigorously until the suspension appears smooth and is consistent in color and texture. The suspended product will be yellow and opaque (see Figure 4).

If foam forms, let the vial stand to allow foam to dissipate.

If the product is not used right away, it should be shaken vigorously to re-suspend. Reconstituted ZYPREXA RELPREVV remains stable for up to 24 hours in the vial.

STEP 4 INJECTING ZYPREXA RELPREVV

Dose	Final Volume to Inject
150 mg	1 mL
210 mg	1.4 mL
300 mg	2 mL
405 mg	2.7 mL

Refer to the table above to determine the final volume to inject. **Suspension concentration is 150 mg/mL ZYPREXA RELPREVV.**

! IMPORTANT

Before administering the injection, confirm there will be someone to accompany the patient after the 3-hour observation period. If this cannot be confirmed, do not give the injection.

- Attach a new safety needle to the syringe.
- Slowly withdraw the desired amount into the syringe.
- !** SOME EXCESS PRODUCT WILL REMAIN IN THE VIAL.
- Engage the needle safety device and remove needle from syringe.
- For administration, select the 19-gauge, 1.5-inch (38 mm) Hypodermic Needle-Pro needle with needle protection device. For obese patients, a 2-inch (50 mm), 19-gauge or larger needle (not included in convenience kit) may be used. **To help prevent clogging, a 19-gauge or larger needle must be used.**
- Attach the new safety needle to the syringe prior to injection. Once the suspension has been removed from the vial, it should be injected immediately.
- !** FOR DEEP, INTRAMUSCULAR GLUTEAL INJECTION ONLY. DO NOT INJECT INTRAVENOUSLY OR SUBCUTANEOUSLY.
- Select and prepare a site for injection in the **gluteal** area.
- After insertion of the needle into the muscle, **!** aspirate for several seconds to ensure that no blood appears. If any blood is drawn into the syringe, discard the syringe and the dose and begin with a new convenience kit. The injection should be performed with steady, continuous pressure.
- !** DO NOT MASSAGE THE INJECTION SITE.
- Engage the needle safety device.
- Dispose of the vials, needles, and syringe appropriately after injection. The vial is for single-use only.

JELCO[®] HYPODERMIC NEEDLE-PRO[®] NEEDLE with NEEDLE PROTECTION DEVICE

1. DESCRIPTION:

The Jelco Hypodermic Needle-Pro device is a sterile, single-use device. It includes a needle and needle safety sheath. The Needle-Pro device can be used with a Luer slip or Luer lock syringe.

2. INDICATIONS FOR USE:

This device is intended for injection or aspiration of fluids. The needle protection device covers the needle after use to help prevent needle sticks.

3. CONTRAINDICATIONS:

None known.

4. WARNINGS:

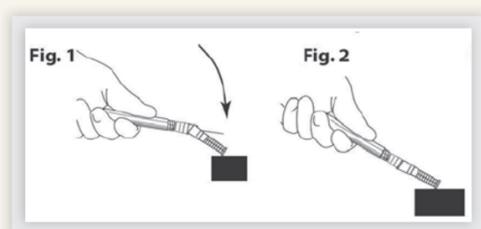
- 4.1 A needle stick with a contaminated needle may cause infectious diseases.
- 4.2 Intentional disengagement of the Needle-Pro device may result in a needle stick with a contaminated needle.
- 4.3 Bent or damaged needles can result in breakage or damage to the tissue or accidental needle puncture. If the needle is bent or damaged, no attempt should be made to straighten the needle or engage the Needle-Pro device. The Needle-Pro device may not properly contain a bent needle and/or the needle could puncture the needle protection device, which may result in a needle stick with a contaminated needle.
- 4.4 Mishandling of the needle protection device may cause needles, especially short or small gauge needles, to bend whereby they protrude from the needle protection sheath, which may result in a contaminated needle-stick.
- 4.5 Do not use with Paraldehyde.

5. CAUTION:

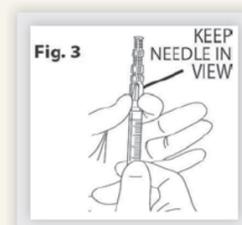
- 5.1 Do Not Reuse: Medical devices require specific material characteristics to perform as intended. These characteristics have been verified for single use only. Any attempt to re-process the device for subsequent re-use may adversely affect the integrity of the device or lead to deterioration in performance.
- 5.2 Follow standard infection control procedures as specified by the Centers for Disease Control and Prevention (USA) or local equivalent.

6. INSTRUCTIONS FOR USE:

- 6.1 Peel blister pouch and remove device.
- 6.2 Attach a syringe (if not already attached) to the Luer connection of the Needle-Pro device with an easy twisting motion. Seat the needle firmly on the Needle-Pro device with a push and a clockwise twist, then pull the needle cap straight away from the needle.
- 6.3 After procedure is completed, press the needle into the sheath using a one-handed technique. Perform a one-handed technique by gently pressing the sheath against a flat surface. As The Sheath Is Pressed (Fig. 1), The Needle Is Firmly Engaged Into The Sheath (Fig. 2).



- 6.4 Visually confirm that the needle is fully engaged into the needle protection sheath.
- 6.5 Only remove the Needle-Pro device with engaged needle from the syringe when required by a specific medical procedure. Remove by grasping the Luer hub of the needle protection device with thumb and forefinger, keeping the free fingers clear of the end of the device containing the needle point (Fig. 3).



- 6.6 After use, place sharps in a suitable sharps container. Dispose of contaminated product in a safe manner according to Centers for Disease Control and Prevention, USA and Federal/State/Local regulations (EPA, OSHA) and health care facility guidelines or local equivalent.

NOTE: Additional dead space added by Needle-Pro device averages 0.036mL.



Caution • Do Not Reuse • Not made with natural rubber latex • Do not use if package is damaged • Sterilized using ethylene oxide • Non-pyrogenic fluid path • Caution: Federal (USA) law restricts this device to sale by or on the order of a physician • Catalogue Number • Batch Code • Date of Manufacture • Use by • Quantity

The Smiths Medical and Jelco design marks; Needle-Pro; and the color orange applied to the needle protection device are trademarks of Smiths Medical. The symbol ® indicates the trademark is registered in the U.S. Patent and Trademark Office and certain other countries.

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Manufacturer:

Smiths Medical ASD Inc.
10 Bowman Drive, Keene, NH 03431 USA
Tel: 1 800 258 5361 (US/CA)
Tel: +1 614 210 7300

www.smiths-medical.com

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Literature revised: August 25, 2014

smiths medical
bringing technology to life

Welcome to the ZYPREXA RELPREVV Patient Care Program

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).

For a tour of the ZYPREXA RELPREVV Patient Care Program system [click here](#).

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ZYPREXA RELPREVV Patient Care Program

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User Name

Password

[Enter](#)

[How Do I Enroll](#)

[FORGOT PASSWORD](#)

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In order to enroll in the ZYPREXA RELPREVV Patient Care Program, you must first complete the required training then submit the appropriate registration form.

ZYprexa **Relprevv**[™]
(olanzapine) For Extended Release
Injectable Suspension

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ZYPREXA RELPREVV Patient Care Program

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ZYPREXA RELPREVV PATIENT CARE PROGRAM CONTACT INFORMATION

ZYPREXA RELPREVV Patient Care Program

Phone: 1-877-772-9390

Fax: 1-877-772-9391

ZYPREXA RELPREVV Patient Care Program Coordinating Center Hours of Operation

Monday – Friday: 8am – 8pm ET

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ZYPREXA RELPREVV Patient Care Program

[On-line Training](#)

ON-LINE TRAINING

Select your role(s) from the list below to access required training

Prescriber

Healthcare Facility Staff

Pharmacy Service Providers (pharmacies and
buy & bill pharmacy service providers)

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ZYPREXA RELPREVV Patient Care Program

Required Prescriber Training

1. **ZYPREXA RELPREVV Patient Care Program Instructions Brochure**
 2. **Healthcare Professional Training** *(select one)*
 - **Slide Presentation**
- OR
- **Recorded Presentation**

ADDITIONAL RESOURCES

Post-Injection Delirium/Sedation Syndrome Case Study Video

Once you have completed the required training, submit the appropriate **registration form**.

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ZYPREXA RELPREVV Patient Care Program

Required Healthcare Facility Staff Training

- **REQUIRED TRAINING FOR STAFF ADMINISTERING INJECTIONS AND STAFF WHO MONITOR PATIENTS**
 1. **Healthcare Professional Training** (*select one*)
 - [Slide Presentation](#)OR
 - [Recorded Presentation](#)
 2. **ZYPREXA RELPREVV Patient Care Program Instructions Brochure**
- **REQUIRED ADDITIONAL TRAINING FOR STAFF ADMINISTERING INJECTIONS**
 3. **Reconstitution & Administration Instruction**
 - [Training Video](#)AND
 - [Poster](#) (view and/or print)

ADDITIONAL RESOURCES

Post-Injection Delirium/Sedation Syndrome Case Study Video

Once all the appropriate staff from a healthcare facility have completed the required training, a representative from the facility must submit the **Healthcare Facility Registration Form**.

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ZYPREXA RELPREVV Patient Care Program

Required Pharmacy Service Provider Training

1. **ZYPREXA RELPREVV Patient Care Program Instructions Brochure**

It is the responsibility of the pharmacy service provider representative to assure that all staff involved with dispensing ZYPREXA RELPREVV have reviewed the ZYPREXA RELPREVV Patient Care Program Instructions Brochure prior to submitting one of the registration forms below.

- **Pharmacy Registration Form**

OR

- **Buy & Bill Pharmacy Service Provider* Registration Form**

* Buy & Bill Pharmacy Service Provider - a licensed healthcare provider that purchases pharmaceuticals through a licensed distributor for its own use in the treatment of a patient and then includes the cost of the pharmaceutical in its billing of patients and third-party payers.

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ZYPREXA RELPREVV Patient Care Program

Registration Forms

Prior to selecting and completing a registration form listed below, please ensure you have completed the appropriate training. To complete training on-line, select the "On-line Training" link below, or to receive materials in hard copy, select the "Order Educational Materials" link below.

Prescriber Registration Form

Pharmacy Registration Form

Buy & Bill Pharmacy Service Provider Registration Form

Patient Registration Form

- *Patient Copy*

Healthcare Facility Registration Form

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Pharmacy Finder

Pharmacy Finder

Use the search option below to locate a **registered** Pharmacy Service Provider.

Search For

By

Name

Search

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Order Educational Materials

To order, please complete the information below and click submit.

Requestor Information

First Name: MI: Last Name:
Address Line 1:
Address Line 2:
City: State: Zip:
Phone: () - Alternate Phone: () -
Fax: () - Email:

Please indicate the number of items requested in the blanks below.

Training Materials Kit for Prescriber* and Healthcare Facility

Kit includes:

- ZYPREXA RELPREVV Patient Care Program Instructions Brochure
- Reconstitution & Administration Poster & Training Video (DVD)
- Healthcare Professional Training Recorded Presentation (DVD) with Participant Guide
- PDSS Case Study Video (DVD)
- Medication Guide
- Prescribing Information

*Note: Patient Materials will automatically ship to a prescriber after prescriber registration is complete.

**Training Material for Pharmacy Service Providers
(traditional pharmacy operation or buy & bill prescriber)**

ZYPREXA RELPREVV Patient Care Program Instructions Brochure

Training Materials Available as Individual Items

ZYPREXA RELPREVV Patient Care Program Instructions Brochure
 Reconstitution & Administration Poster
 Reconstitution & Administration Training Video (DVD)
 Healthcare Professional Training Recorded Presentation (DVD) with participant guide
 PDSS Case Study Video (DVD)
Patient Materials
 10 Wristbands
 10 ID cards

Forms Available as Individual Items:

Single Patient Injection Form - tear-off pad of forms (25 forms/pad)
 Multiple Patient Injection Form - tear-off pad of forms (25 forms/pad)
 PDSS Form - 3 forms/pack
 Patient Registration Form - 5 patient forms/pack

I understand that any personal information provided on this form will be used to provide educational materials only. For further privacy information please see the [Privacy Policy](#).

Submit

You may also contact your Lilly sales representative to request materials and resources.

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MITCHELL V Mathis
12/19/2014