

**ZYPREXA<sup>®</sup>Relprevv<sup>™</sup>**  
*(olanzapine) For Extended Release  
Injectable Suspension*



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

## **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.**

Patient injection data should only be completed either via the Single Patient Injection Form or the Multiple Patient Injection Form. Do not use both forms for an individual injection; this will result in duplicate reporting.

### **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.

## Table of Contents

Introduction to ZYPREXA RELPREVV Patient Care Program .....	2
Patient Care Program Overview .....	2
Patient Care Program Contact Information .....	4
Prescriber Information .....	5
Prescriber Enrollment .....	5
Patient Enrollment .....	6
Patient Care Program Data Entry .....	6
Healthcare Facility Information .....	7
Healthcare Facility Enrollment .....	7
Healthcare Facility Representative .....	7
Pharmacy Service Provider Information .....	9
Pharmacy Service Provider Enrollment .....	9
Ordering ZYPREXA RELPREVV .....	9
Dispensing ZYPREXA RELPREVV .....	9
Glossary of Terms .....	12

# 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.

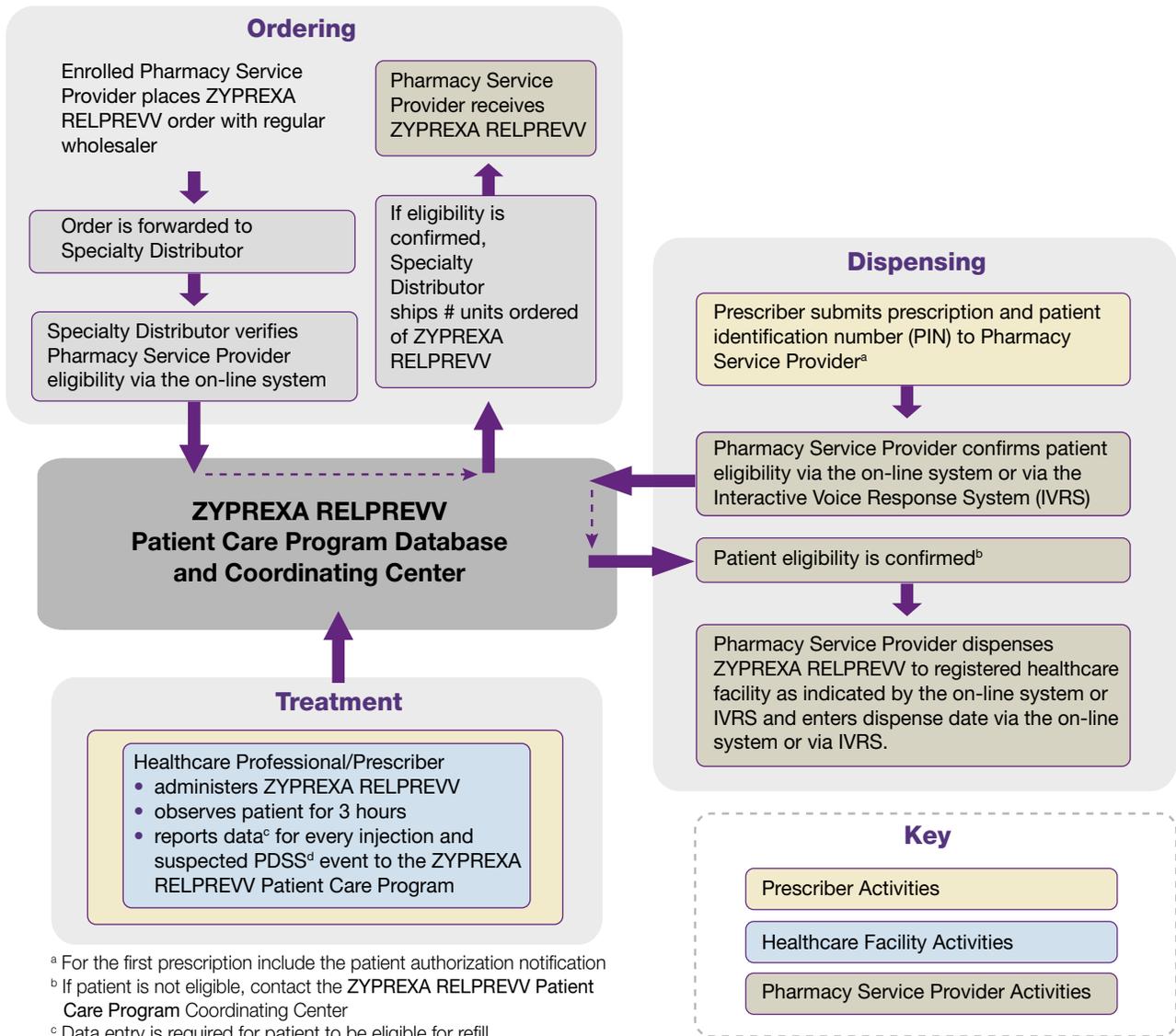
Increased Mortality in Elderly Patients with Dementia-Related Psychosis — Elderly patients with dementia related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical 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<sup>®</sup>Relprevv<sup>™</sup>**  
*(olanzapine) For Extended Release  
 Injectable Suspension*

**ZYPREXA RELPREVV Patient Care Program Enrollment**

<p><b>Prescriber</b></p> <ul style="list-style-type: none"> <li>• Reviews educational materials</li> <li>• Submits enrollment form to ZYPREXA RELPREVV Patient Care Program Coordinating Center</li> </ul>	<p><b>Healthcare Facility</b></p> <ul style="list-style-type: none"> <li>• Ensures staff are trained and facility can comply with conditions of safe use</li> <li>• Submits enrollment form to ZYPREXA RELPREVV Patient Care Program Coordinating Center</li> <li>• Receives &amp; stores patient authorization notification</li> </ul>	<p><b>Patient</b></p> <p>To enroll patient, prescriber:</p> <ul style="list-style-type: none"> <li>• Reviews risks of ZYPREXA RELPREVV with patient</li> <li>• Obtain signature of patient or legal guardian OR check box if court order of involuntary commitment</li> <li>• Submits enrollment form to ZYPREXA RELPREVV Patient Care Program Coordinating Center</li> <li>• Receives &amp; stores patient authorization notification</li> </ul>	<p><b>Pharmacy Service Provider</b></p> <ul style="list-style-type: none"> <li>• Reviews ZYPREXA RELPREVV Patient Care Program materials</li> <li>• Ensures pharmacy staff are trained</li> <li>• Submits enrollment form to ZYPREXA RELPREVV Patient Care Program Coordinating Center</li> </ul>
--	---	---	---

**ZYPREXA RELPREVV Patient Care Program Process Flow**



<sup>a</sup> For the first prescription include the patient authorization notification  
<sup>b</sup> If patient is not eligible, contact the ZYPREXA RELPREVV Patient Care Program Coordinating Center  
<sup>c</sup> Data entry is required for patient to be eligible for refill  
<sup>d</sup> 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 Fax:**

1-877-772-9391

**Via Internet:**

[www.zyprexarelpvprogram.com](http://www.zyprexarelpvprogram.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.zyprexareprevvprogram.com](http://www.zyprexareprevvprogram.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 the Safety Call Center at 1-866-770-9010 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://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](http://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](http://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](http://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 vial 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.zyprexarelpbevprogram.com](http://www.zyprexarelpbevprogram.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](http://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 vial 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 vial 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 vial 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.





# 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 will comply with audits by the manufacturer or a third party acting on behalf of the manufacturer to ensure all processes and procedures are in place and being followed.
- I will maintain records of all processes and procedures including compliance with those processes and procedures.

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 CHEPLAPHARM will regularly evaluate ZYPREXA RELPREVV Patient Care Program compliance to ensure that program objectives are met. CHEPLAPHARM 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 CHEPLAPHARM 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

Version 4.0 02Oct2023

CONFIDENTIAL

Page 2 of 2



# MULTIPLE 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 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:	____ - ____ - ____ month      day      year	____ - ____ - ____ month      day      year	____ - ____ - ____ month      day      year
PDSS since last visit? (check one)	Yes      No If Yes, has the prescriber been notified of the PDSS event? Yes      No	Yes      No If Yes, has the prescriber been notified of the PDSS event? Yes      No	Yes      No If Yes, has the prescriber been notified of the PDSS event? Yes      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"/> : <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> : <input type="text"/> <input type="text"/>
Dose of Injection (check one)	150 mg      210 mg 300 mg      405 mg Other dose _____ mg	150 mg      210 mg 300 mg      405 mg Other dose _____ mg	150 mg      210 mg 300 mg      405 mg Other dose _____ mg
Observed at least 3 hours post-injection? (check one)	Yes      No	Yes      No	Yes      No
PDSS during onsite observation? (check one)	Yes      No If Yes, has the prescriber been notified of the PDSS event? Yes      No	Yes      No If Yes, has the prescriber been notified of the PDSS event? Yes      No	Yes      No 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? (check one)	Yes      No	Yes      No	Yes      No
Following the injection, was the patient accompanied from the facility? (check one)	Yes      No Not applicable, patient did not leave facility (in-patient)	Yes      No Not applicable, patient did not leave facility (in-patient)	Yes      No 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?	Yes      No	Yes      No	Yes      No



# 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: \_\_\_\_\_

PHONE 1-877-772-9390                      FAX 1-877-772-9391                      www.zyprexarelprevvprogram.com



# PATIENT REGISTRATION FORM

## PATIENT AGREEMENT

The maker of ZYPREXA RELPREVV, CHEPLAPHARM 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 CHEPLAPHARM 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

www.zyprexarelprevvprogram.com



# PATIENT REGISTRATION FORM 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, CHEPLAPHARM 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 CHEPLAPHARM 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.

PHONE 1-877-772-9390 FAX 1-877-772-9391 www.zyprexarelprevvprogram.com





# POST-INJECTION DELIRIUM/SEDATION SYNDROME (PDSS) FORM

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

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

Time of ZYPREXA RELPREVV Injection:   :    
 24-hour clock

Convenience Kit Package

Lot # \_\_\_\_\_

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

- |                 |                             |  |
|-----------------|-----------------------------|--|
| 1 - 15 minutes  | 46 - 60 minutes             | 121 - 150 minutes (2 ½ hours)                    |
| 16 - 30 minutes | 61 - 90 minutes (1 ½ hours) | 151 - 180 minutes (3 hours)                      |
| 31 - 45 minutes | 91 - 120 minutes (2 hours)  | If greater than 3 hours please specify:<br>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).

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

Phone 1-877-772-9390 FAX 1-877-772-9391 www.zyprexarelprevvprogram.com



# 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

- |                      |           |                                    |                       |
|----------------------|-----------|------------------------------------|-----------------------|
| Assisted ventilation | EEG       | MRI                                | Urine drug screen     |
| Brain CT             | IV fluids | Observation/symptomatic management | Vital sign monitoring |
| ECG                  | Labs      | Restraints                         | 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		
			Day	Months	Years
			Day	Months	Years
			Day	Months	Years
			Day	Months	Years
			Day	Months	Years

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

- |                               |              |               |               |
|-------------------------------|--------------|---------------|---------------|
| Alcohol                       | Barbiturates | Cocaine       | Opiates       |
| Amphetamines/Methamphetamines | Cannabinoid  | Hallucinogens | Phencyclidine |

Event reported by: \_\_\_\_\_  
First MI Last

Title/Occupation: \_\_\_\_\_

If agent of the Prescriber, 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): \_\_\_\_\_





## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ZYPREXA RELPREV (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 RELPREV is available only through a restricted distribution program called ZYPREXA RELPREV Patient Care Program and requires prescriber, healthcare facility, patient, and pharmacy enrollment. (2.1, 5.1, 5.2, 10.2, 17)
- 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. (5.3, 8.5, 17)

### RECENT MAJOR CHANGES

Warnings and Precautions, Tardive Dyskinesia (5.8)	10/2019
Warnings and Precautions, Use in Patients with Concomitant Illness (5.16)	Removed 4/2020
Warnings and Precautions, Anticholinergic (antimuscarinic) Effects (5.16)	4/2020

### INDICATIONS AND USAGE

ZYPREXA<sup>®</sup> RELPREV™ 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 RELPREV 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 RELPREV. (2.1)
- Establish tolerability with oral olanzapine prior to initiating treatment. (2.1)
- ZYPREXA RELPREV 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 RELPREV provided in the convenience kit. (2.2)

### DOSAGE FORMS AND STRENGTHS

Powder for suspension for single-dose 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)
- *Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)*: Discontinue if DRESS is suspected. (5.6)
- *Metabolic Changes*: Atypical antipsychotic drugs have been associated with metabolic changes including hyperglycemia, dyslipidemia, and weight gain. (5.7)
  - *Hyperglycemia and Diabetes Mellitus*: 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. (5.7)
  - *Dyslipidemia*: 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. (5.7)
- *Tardive Dyskinesia*: Discontinue if clinically appropriate. (5.8)
- *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. (5.9)
- *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 RELPREV 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)
- *Anticholinergic (antimuscarinic) Effects*: Use with caution with other anticholinergic drugs and in patients with urinary retention, prostatic hypertrophy, constipation, paralytic ileus or related conditions. (5.16, 7.1)
- *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 RELPREV 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 the Safety Call Center at 1-866-770-9010 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://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*: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. (8.1)
- *Pediatric Use*: Safety and effectiveness of ZYPREXA RELPREV in children <18 years of age have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2023

## FULL PRESCRIBING INFORMATION: CONTENTS\*

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

#### 1 INDICATIONS AND USAGE

- 1.1 Schizophrenia

#### 2 DOSAGE AND ADMINISTRATION

- 2.1 Dosage  
2.2 Instructions to Reconstitute and Administer ZYPREXA RELPREV

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

- 5.1 Post-Injection Delirium/Sedation Syndrome  
5.2 Prescribing and Distribution Program for ZYPREXA RELPREV  
5.3 Elderly Patients with Dementia-Related Psychosis  
5.4 Suicide  
5.5 Neuroleptic Malignant Syndrome (NMS)  
5.6 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)  
5.7 Metabolic Changes  
5.8 Tardive Dyskinesia  
5.9 Orthostatic Hypotension  
5.10 Falls  
5.11 Leukopenia, Neutropenia, and Agranulocytosis  
5.12 Dysphagia  
5.13 Seizures  
5.14 Potential for Cognitive and Motor Impairment

- 5.15 Body Temperature Regulation

- 5.16 Anticholinergic (antimuscarinic) Effects

- 5.17 Hyperprolactinemia

- 5.18 Laboratory Tests

#### 6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience  
6.2 Postmarketing Experience

#### 7 DRUG INTERACTIONS

- 7.1 Potential for Other Drugs to Affect Olanzapine  
7.2 Potential for Olanzapine to Affect Other Drugs

#### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy  
8.2 Lactation  
8.3 Females and Males of Reproductive Potential  
8.4 Pediatric Use  
8.5 Geriatric Use

#### 9 DRUG ABUSE AND DEPENDENCE

- 9.3 Dependence

#### 10 OVERDOSAGE

- 10.1 Human Experience  
10.2 Management of Overdose

#### 11 DESCRIPTION

#### 12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action  
12.2 Pharmacodynamics  
12.3 Pharmacokinetics

#### 13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility  
13.2 Animal Toxicology and/or Pharmacology

#### 14 CLINICAL STUDIES

- 14.1 Schizophrenia

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

- 16.1 How Supplied  
16.2 Storage and Handling

#### 17 PATIENT COUNSELING INFORMATION

\* Sections or subsections omitted from the full prescribing information are not listed.

ZYPREXA RELPREV (olanzapine)  
For Extended Release Injectable Suspension

ZYPREXA RELPREV (olanzapine)  
For Extended Release Injectable Suspension

ZYPREXA RELPREV (olanzapine)  
For Extended Release Injectable Suspension

**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)*].

**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), Use in Specific Populations (8.5) and Patient Counseling Information (17)*].

**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*

ZYPREXA RELPREVV (olanzapine)  
For Extended Release Injectable Suspension

*Overdosage (10.1)*. Patients should be informed of this risk and how to recognize related symptoms [see *Patient Counseling Information (17)*]. 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 in 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. 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 (5.18), 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 (5.7)*].

**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.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

**Step 1: Preparing Materials**

Convenience kit includes:

- Single-dose 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.

ZYPREXA RELPREVV (olanzapine)  
For Extended Release Injectable Suspension

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.

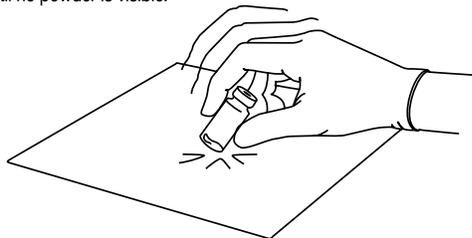


Figure 1: Tap firmly to mix.

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).

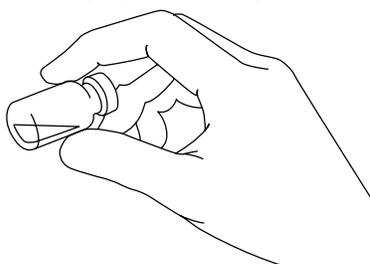


Figure 2: Check for unsuspended powder and repeat tapping if needed.

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).

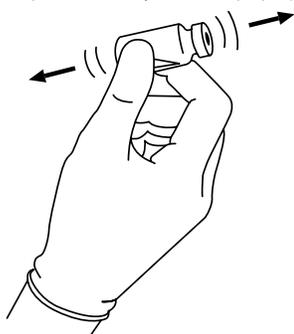


Figure 3: Vigorously shake vial.

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 RELPREVV remains stable at room temperature for up to 24 hours in the vial.

#### Step 4: Injecting ZYPREXA RELPREVV

**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 150 mg/mL 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

Attach a new safety needle to the syringe.

Slowly withdraw the desired amount into the syringe.

**Some excess product will remain in the vial.**

ZYPREXA RELPREVV (olanzapine)  
For Extended Release Injectable Suspension

Engage the needle safety device and remove the 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-dose only.

### 3 DOSAGE FORMS AND STRENGTHS

ZYPREXA RELPREVV is a powder for suspension for intramuscular use only.

ZYPREXA RELPREVV is present as a yellow solid in a glass vial equivalent to 210, 300, or 405 mg olanzapine single-dose 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 RELPREVV, 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 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 RELPREVV [see Patient Counseling Information (17)].

#### 5.2 Prescribing and Distribution Program for ZYPREXA RELPREVV

ZYPREXA RELPREVV is available only through a restricted distribution program [see Boxed Warning, Indications and Usage (1), and Patient Counseling Information (17)]. 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.

ZYPREXA RELPREVV 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 RELPREVV 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 RELPREVV is not approved for the treatment of patients with dementia-related psychosis [see Boxed Warning, Use in Specific Populations (8.5), and Patient Counseling Information (17)].**

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

ZYPREXA RELPREVV (olanzapine)  
For Extended Release Injectable Suspension

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 RELPREVV is not approved for the treatment of patients with dementia-related psychosis [see *Boxed Warning and Patient Counseling Information* (17)].

#### 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 RELPREVV [see *Dosage and Administration* (2.1)]. The patient should be carefully monitored, since recurrences of NMS have been reported [see *Patient Counseling Information* (17)].

#### 5.6 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported with olanzapine exposure. DRESS may present with a cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, and/or lymphadenopathy with systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and/or pericarditis. DRESS is sometimes fatal. Discontinue ZYPREXA RELPREVV if DRESS is suspected [see *Patient Counseling Information* (17)].

#### 5.7 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes including hyperglycemia, dyslipidemia, and weight gain. Metabolic changes may be associated with increased cardiovascular/cerebrovascular risk. Olanzapine's specific metabolic profile is presented below.

#### Hyperglycemia and Diabetes Mellitus

Healthcare providers 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)].

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  $\geq 200$  mg/dL, and/or a baseline fasting glucose level  $\geq 126$  mg/dL).

ZYPREXA RELPREVV (olanzapine)  
For Extended Release Injectable Suspension

Olanzapine-treated patients had a greater mean HbA<sub>1c</sub> increase from baseline of 0.04% (median exposure 21 days), compared to a mean HbA<sub>1c</sub> 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 $\geq 126$ mg/dL)	Olanzapine	543	2.2%	345	12.8%
		Placebo	293	3.4%	NA <sup>a</sup>	NA <sup>a</sup>
	Borderline to High ( $\geq 100$ mg/dL and <126 mg/dL to $\geq 126$ mg/dL)	Olanzapine	178	17.4%	127	26.0%
		Placebo	96	11.5%	NA <sup>a</sup>	NA <sup>a</sup>

<sup>a</sup> 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 RELPREVV 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 $\geq 126$ mg/dL)	Olanzapine	124	0%	108	0.9%
		Placebo	53	1.9%	NA <sup>a</sup>	NA <sup>a</sup>
	Borderline to High ( $\geq 100$ mg/dL and <126 mg/dL to $\geq 126$ mg/dL)	Olanzapine	14	14.3%	13	23.1%
		Placebo	13	0%	NA <sup>a</sup>	NA <sup>a</sup>

<sup>a</sup> Not Applicable.

#### Dyslipidemia

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)].

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.

ZYPREXA RELPREVV (olanzapine)  
For Extended Release Injectable Suspension

**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 <sup>a</sup>	NA <sup>a</sup>
	Normal to High (<150 mg/dL to ≥200 mg/dL)	Olanzapine	457	9.2%	293	32.4%
		Placebo	251	4.4%	NA <sup>a</sup>	NA <sup>a</sup>
	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 <sup>a</sup>	NA <sup>a</sup>
Fasting Total Cholesterol	Increase by ≥40 mg/dL	Olanzapine	745	21.6%	489	32.9%
		Placebo	402	9.5%	NA <sup>a</sup>	NA <sup>a</sup>
	Normal to High (<200 mg/dL to ≥240 mg/dL)	Olanzapine	392	2.8%	283	14.8%
		Placebo	207	2.4%	NA <sup>a</sup>	NA <sup>a</sup>
	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 <sup>a</sup>	NA <sup>a</sup>
Fasting LDL Cholesterol	Increase by ≥30 mg/dL	Olanzapine	536	23.7%	483	39.8%
		Placebo	304	14.1%	NA <sup>a</sup>	NA <sup>a</sup>
	Normal to High (<100 mg/dL to ≥160 mg/dL)	Olanzapine	154	0%	123	7.3%
		Placebo	82	1.2%	NA <sup>a</sup>	NA <sup>a</sup>
	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 <sup>a</sup>	NA <sup>a</sup>

<sup>a</sup> 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.

Dose group differences with respect to increases in fasting triglycerides have been observed. In a 24-week randomized, double-blind, fixed-dose study with ZYPREXA RELPREVV, statistically significant differences among dose groups have been observed for fasting triglycerides. Incidence of changes from normal to high levels of fasting triglycerides at any time during the trial indicated significant differences between the highest dose group (300 mg/2 weeks, 24.5% [13/53]) and the lower dose groups (150 mg/2 weeks, 6.5% [4/62]; 405 mg/4 weeks, 9.8% [13/133]).

**Olanzapine Monotherapy in Adolescents** — The safety and efficacy of ZYPREXA RELPREVV 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.

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 <sup>a</sup>	NA <sup>a</sup>
	Normal to High (<90 mg/dL to >130 mg/dL)	Olanzapine	67	26.9%	66	36.4%
		Placebo	28	10.7%	NA <sup>a</sup>	NA <sup>a</sup>
	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 <sup>a</sup>	NA <sup>a</sup>

ZYPREXA RELPREVV (olanzapine)  
For Extended Release Injectable Suspension

**Table 5: Changes in Fasting Lipids Values from Adolescent Oral Olanzapine Monotherapy Studies (Cont.)**

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 Total Cholesterol	Increase by ≥40 mg/dL	Olanzapine	138	14.5%	122	14.8%
		Placebo	66	4.5%	NA <sup>a</sup>	NA <sup>a</sup>
	Normal to High (<170 mg/dL to ≥200 mg/dL)	Olanzapine	87	6.9%	78	7.7%
		Placebo	43	2.3%	NA <sup>a</sup>	NA <sup>a</sup>
	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 <sup>a</sup>	NA <sup>a</sup>
Fasting LDL Cholesterol	Increase by ≥30 mg/dL	Olanzapine	137	17.5%	121	22.3%
		Placebo	63	11.1%	NA <sup>a</sup>	NA <sup>a</sup>
	Normal to High (<110 mg/dL to ≥130 mg/dL)	Olanzapine	98	5.1%	92	10.9%
		Placebo	44	4.5%	NA <sup>a</sup>	NA <sup>a</sup>
	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 <sup>a</sup>	NA <sup>a</sup>

<sup>a</sup> Not Applicable.

**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)].

**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

Dose group differences with respect to weight gain have been observed in some studies. In a 24-week randomized, double-blind, fixed-dose study with ZYPREXA RELPREVV, mean baseline-to-endpoint increase in weight (150 mg/2 weeks, n=140: 0.67 kg; 405 mg/4 weeks, n=315: 0.89 kg; 300 mg/2 weeks, n=140: 1.70 kg) was observed with significant differences between the lowest and highest dose groups (150 vs 300 mg/2 weeks). 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 adult patients with schizophrenia or schizoaffective disorder, 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.

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

ZYPREXA RELPREVV (olanzapine)  
For Extended Release Injectable Suspension

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 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

### 5.8 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.

Tardive dyskinesia 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.

### 5.9 Orthostatic Hypotension

ZYPREXA RELPREVV may induce orthostatic hypotension associated with dizziness, tachycardia, bradycardia and, in some patients, syncope, probably reflecting its  $\alpha_1$ -adrenergic antagonistic properties [see Patient Counseling Information (17)]. Syncope-related adverse reactions were reported in 0.1% of patients treated with ZYPREXA RELPREVV in clinical studies.

ZYPREXA RELPREVV (olanzapine)  
For Extended Release Injectable Suspension

From an analysis of the vital sign data in an integrated database of 41 completed clinical studies in adult patients treated with oral olanzapine, orthostatic hypotension was recorded in  $\geq 20\%$  (1277/6030) of patients.

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 RELPREVV [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)].

### 5.10 Falls

ZYPREXA RELPREVV may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

### 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 RELPREVV 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  $< 1000/\text{mm}^3$ ) should discontinue ZYPREXA RELPREVV 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 RELPREVV, 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 RELPREVV treatment, occurring at an incidence of 8% in ZYPREXA RELPREVV patients compared to 2% in placebo patients. Somnolence and sedation adverse reactions led to discontinuation in 0.6% of patients in the premarketing ZYPREXA RELPREVV 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)].

### 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 RELPREVV 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)].

### 5.16 Anticholinergic (antimuscarinic) Effects

Olanzapine exhibits in vitro muscarinic receptor affinity [see Clinical Pharmacology 12.2]. 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 a current diagnosis or prior history of urinary retention, clinically significant prostatic hypertrophy, constipation, or a history of paralytic ileus or related conditions. In post marketing experience, the risk for severe adverse reactions (including fatalities) was increased with concomitant use of anticholinergic medications [see Drug Interactions (7.1)].

### 5.17 Hyperprolactinemia

As with other drugs that antagonize dopamine  $D_2$  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

ZYPREXA RELPREVV (olanzapine)  
For Extended Release Injectable Suspension

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 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 events<sup>1</sup> (2% [49/3240] of females), sexual function-related events<sup>2</sup> (2% [150/8136] of females and males), and breast-related events<sup>3</sup> (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 events<sup>1</sup> (1% [2/168] of females), sexual function-related events<sup>2</sup> (0.7% [3/454] of females and males), and breast-related events<sup>3</sup> (2% [3/168] of females, 2% [7/286] of males) [see *Use in Specific Populations (8.4)*].

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

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

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

Dose group differences with respect to prolactin elevation have been observed in some studies. In a 24-week randomized, double-blind, fixed-dose study with ZYPREXA RELPREVV, statistically significant differences among dose groups were observed for prolactin levels, with a mean baseline-to-endpoint increase observed in the highest dose group (300 mg/2 weeks, n=115: 3.57 ng/mL) relative to mean decreases in the lower dose groups (150 mg/2 weeks, n=109: -5.61 ng/mL; 405 mg/4 weeks, n=259: -2.76 ng/mL). 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 adult patients with schizophrenia or schizoaffective disorder, incidence of 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%) indicated significant differences between 10 vs 40 mg/day and 20 vs 40 mg/day.

## 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 (5.7) and Patient Counseling Information (17)*].

## 6 ADVERSE REACTIONS

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect or predict the rates observed in practice.

The information below for ZYPREXA RELPREVV is derived primarily from a clinical trial database consisting of 2058 patients with approximately 1948 patient years of exposure to ZYPREXA RELPREVV. 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 RELPREVV, the MedDRA terminology has been used to classify reported adverse reactions. Data obtained from oral olanzapine studies was reported using the COSTART and MedDRA dictionaries.

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 RELPREVV.

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 healthcare provider with some basis for estimating the relative contribution of drug and nondrug factors to the adverse reaction incidence in the population studied.

ZYPREXA RELPREVV (olanzapine)  
For Extended Release Injectable Suspension

## 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)
<b>Ear and Labyrinth Disorders</b>				
Ear pain	2	1	1	4
<b>Gastrointestinal Disorders</b>				
Abdominal pain <sup>a</sup>	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
<b>General Disorders and Administration Site Conditions</b>				
Fatigue	2	4	2	3
Injection site pain	0	2	3	2
Pain	0	0	2	3
Pyrexia	0	2	0	0
<b>Infections and Infestations</b>				
Nasopharyngitis	2	3	6	1
Tooth infection <sup>b</sup>	0	4	0	0
Upper respiratory tract infection	2	3	1	4
Viral infection	0	0	0	2
<b>Injury, Poisoning and Procedural Complications</b>				
Procedural pain	0	2	0	0
<b>Investigations</b>				
Electrocardiogram QT-corrected interval prolonged	1	0	0	2
Hepatic enzyme increased <sup>c</sup>	1	4	1	3
Weight increased	5	5	6	7
<b>Metabolism and Nutrition Disorders</b>				
Increased appetite	0	1	4	6
<b>Musculoskeletal and Connective Tissue Disorders</b>				
Arthralgia	0	3	3	3
Back pain	4	4	3	5
Muscle spasms	0	3	1	2
Musculoskeletal stiffness	1	1	4	4
<b>Nervous System Disorders</b>				
Dizziness	2	4	4	1
Dysarthria	0	0	1	2
Headache <sup>d</sup>	8	13	15	18
Sedation <sup>e</sup>	7	13	8	13
Tremor	1	3	0	1
<b>Psychiatric Disorders</b>				
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

ZYPREXA RELPREVV (olanzapine)  
For Extended Release Injectable Suspension

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

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)
<b>Reproductive System and Breast Disorders</b>				
Vaginal discharge	0	0	4	4
<b>Respiratory, Thoracic and Mediastinal Disorders</b>				
Cough	5	3	5	9
Nasal congestion <sup>f</sup>	3	2	1	7
Pharyngolaryngeal pain	2	2	3	3
Sneezing	0	0	0	2
<b>Skin and Subcutaneous Tissue Disorders</b>				
Acne	0	2	0	2
<b>Vascular Disorders</b>				
Hypertension	0	3	2	0

<sup>a</sup> The term abdominal pain upper was combined under abdominal pain.

<sup>b</sup> The term tooth abscess was combined under tooth infection.

<sup>c</sup> The terms alanine aminotransferase increased, aspartate aminotransferase increased, and gamma-glutamyltransferase increased were combined under hepatic enzyme increased.

<sup>d</sup> The term tension headache was combined under headache.

<sup>e</sup> The term somnolence was combined under sedation.

<sup>f</sup> The term sinus congestion was combined under nasal congestion.

#### Dose Dependency of Adverse Reactions

Dose group differences have been observed for weight, fasting triglycerides and prolactin elevation for ZYPREXA RELPREVV [see *Warnings and Precautions* (5.7, 5.17)].

A dose group difference for oral olanzapine has been observed for fatigue, dizziness, weight gain and prolactin elevation. 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 adult patients with schizophrenia or schizoaffective disorder, incidence of fatigue (10 mg/day: 1.5%; 20 mg/day: 2.1%; 40 mg/day: 6.6%) was observed with significant differences between 10 vs 40 and 20 vs 40 mg/day. The incidence of dizziness (10 mg/day: 2.6%; 20 mg/day: 1.6%; 40 mg/day: 6.6%) was observed with significant differences between 20 vs 40 mg. Dose group differences were also noted for weight gain and prolactin elevation [see *Warnings and Precautions* (5.7, 5.17)].

#### 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 10: 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 <sup>a</sup>	15	14	12	14
Akathisia <sup>b</sup>	23	16	19	27

<sup>a</sup> Percentage of patients with a Simpson-Angus Scale total score >3.

<sup>b</sup> 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 11: 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 <sup>a</sup>	1	3	2	3
Parkinsonism events <sup>b</sup>	10	8	14	20
Akathisia events <sup>c</sup>	1	5	11	10
Dyskinetic events <sup>d</sup>	4	0	2	1

ZYPREXA RELPREVV (olanzapine)  
For Extended Release Injectable Suspension

**Table 11: 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 (Cont.)**

	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)
Residual events <sup>a</sup>	1	2	5	1
Any extrapyramidal event	16	15	25	32

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

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

<sup>c</sup> Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.

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

<sup>e</sup> 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.

#### Other Adverse Reactions

##### 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).

##### Other Adverse Reactions Observed During the Clinical Trial Evaluation of Olanzapine for Extended-Release Injectable Suspension

Injection site abscess has been reported in clinical trials with ZYPREXA RELPREVV therapy. Isolated cases required surgical intervention.

##### 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 attempt<sup>1</sup>; *Rare:* chills and fever, hangover effect, sudden death<sup>1</sup>.

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

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

**Hemic and Lymphatic System** – *Infrequent:* thrombocytopenia.

**Metabolic and Nutritional Disorders** – *Frequent:* alkaline phosphatase increased; *Infrequent:* 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:* amenorrhea<sup>2</sup>, breast pain, decreased menstruation, impotence<sup>2</sup>, increased menstruation<sup>2</sup>, menorrhagia<sup>2</sup>, metrorrhagia<sup>2</sup>, polyuria<sup>2</sup>, urinary frequency, urinary retention, urinary urgency, urination impaired.

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

<sup>2</sup> Adjusted for gender.

ZYPREXA RELPREVV (olanzapine)  
For Extended Release Injectable Suspension

## Vital Signs and Laboratory Studies

### Laboratory Changes

**ZYPREXA RELPREVV in Adults:** Statistically significant within group mean changes for ZYPREXA RELPREVV, 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 RELPREVV 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 RELPREVV, 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.

From an analysis of the laboratory data in an integrated database of 41 completed clinical studies in adult patients treated with oral olanzapine, high GGT levels were recorded in  $\geq 1\%$  (88/5245) of patients.

Statistically significant differences were observed between ZYPREXA RELPREVV and oral olanzapine for the incidence of treatment-emergent low platelet count (0% ZYPREXA RELPREVV vs 1% oral olanzapine); and low total bilirubin (2.8% ZYPREXA RELPREVV vs 0.7% for oral olanzapine). There was a statistically significant difference between ZYPREXA RELPREVV and oral olanzapine in potentially clinically significant changes for high leukocyte count (0% ZYPREXA RELPREVV vs 1% oral olanzapine).

Changes in aminotransferases observed with ZYPREXA RELPREVV treatment were similar to those reported with ZYPREXA treatment. In placebo-controlled ZYPREXA RELPREVV studies, clinically significant ALT elevations ( $\geq 3$  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 RELPREVV database of 1886 patients with baseline ALT  $\leq 90$  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 RELPREVV treatment was continued.

From an analysis of the laboratory data in an integrated database of 41 completed clinical studies in adult patients treated with oral olanzapine, elevated uric acid was recorded in  $\geq 3\%$  (171/4641) of patients.

**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  $\leq 90$  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  $\geq 3$  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  $\geq 5$  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.

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 RELPREVV 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)].

## 6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ZYPREXA and ZYPREXA RELPREVV. Because these reactions are reported voluntarily from a population of uncertain size, it is difficult to reliably estimate their frequency or evaluate a causal relationship to drug exposure.

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), cholestatic or mixed liver injury, diabetic coma, diabetic ketoacidosis, discontinuation reaction (diaphoresis, nausea, or vomiting), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), hepatitis, jaundice, neutropenia, pancreatitis, priapism, rash, restless legs syndrome, rhabdomyolysis, salivary hypersecretion, stuttering<sup>1</sup>, and venous thromboembolic events (including pulmonary embolism and deep venous thrombosis). Random cholesterol levels of  $\geq 240$  mg/dL and random triglyceride levels of  $\geq 1000$  mg/dL have been reported. Additionally, injection site abscess has been reported in postmarketing reports with ZYPREXA RELPREVV therapy. Isolated cases required surgical intervention.

<sup>1</sup> Stuttering was only studied in oral and long acting injection (LAI) formulations.

## 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

ZYPREXA RELPREVV (olanzapine)

For Extended Release Injectable Suspension

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.

**Anticholinergic Drugs** — Concomitant treatment with olanzapine and other drugs with anticholinergic activity can increase the risk for severe gastrointestinal adverse reactions related to hypomotility. ZYPREXA RELPREVV should be used with caution in patients receiving medications having anticholinergic (antimuscarinic) effects [see *Warnings and Precautions* (5.16)].

## 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

#### Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to atypical antipsychotics, including ZYPREXA RELPREVV, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visit <http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/>.

#### Risk Summary

Neonates exposed to antipsychotic drugs, including ZYPREXA RELPREVV, during the third trimester are at risk for extrapyramidal and/or withdrawal symptoms following delivery (see *Clinical Considerations*). Overall available data from published epidemiologic studies of pregnant women exposed to olanzapine have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes (see *Data*). There are risks to the mother associated with untreated schizophrenia or bipolar I disorder and with exposure to antipsychotics, including ZYPREXA RELPREVV, during pregnancy (see *Clinical Considerations*).

Olanzapine was not teratogenic when administered orally to pregnant rats and rabbits at doses that are 9- and 30-times the daily oral maximum recommended human dose (MRHD), based on mg/m<sup>2</sup> body surface area; some fetal toxicities were observed at these doses (see *Data*).

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

#### Clinical Considerations

##### Disease-associated maternal and embryo/fetal risk

There is a risk to the mother from untreated schizophrenia or bipolar I disorder, including increased risk of relapse, hospitalization, and suicide. Schizophrenia and bipolar I disorder are associated with increased adverse perinatal outcomes, including preterm birth. It is not known if this is a direct result of the illness or other comorbid factors.

ZYPREXA RELPREVV (olanzapine)

For Extended Release Injectable Suspension

### Fetal/Neonatal adverse reactions

Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs, including ZYPREXA RELPREVV, during the third trimester of pregnancy. These symptoms have varied in severity. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization.

### Data

#### Human Data

Placental passage has been reported in published study reports; however, the placental passage ratio was highly variable ranging between 7% to 167% at birth following exposure during pregnancy. The clinical relevance of this finding is unknown.

Published data from observational studies, birth registries, case reports and meta-analyses that have evaluated the use of atypical antipsychotics during pregnancy do not establish an increased risk of major birth defects. A retrospective cohort study from a Medicaid database of 9258 women exposed to antipsychotics during pregnancy did not indicate an overall increased risk for major birth defects.

#### Animal Data

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 daily oral MRHD based on mg/m<sup>2</sup> body surface area, 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 daily oral MRHD based on mg/m<sup>2</sup> body surface area), and gestation was prolonged at 10 mg/kg/day (5 times the daily oral MRHD based on mg/m<sup>2</sup> body surface area). 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 daily oral MRHD based on mg/m<sup>2</sup> body surface area). No evidence of teratogenicity or embryo-fetal toxicity was observed in rats or rabbits with olanzapine at intramuscular doses up to 75 mg/kg (1 and 2 times the MRHD of 300 mg every 2 weeks, respectively, based on mg/m<sup>2</sup> body surface area).

## 8.2 Lactation

### Risk Summary

Olanzapine pamoate is present in human milk. There are reports of excess sedation, irritability, poor feeding, and extrapyramidal symptoms (tremors and abnormal muscle movements) in infants exposed to olanzapine pamoate through breast milk (see *Clinical Considerations*). There is no information on the effects of olanzapine pamoate on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZYPREXA RELPREVV and any potential adverse effects on the breastfed child from ZYPREXA RELPREVV or from the mother's underlying condition.

### Clinical Considerations

Infants exposed to ZYPREXA RELPREVV should be monitored for excess sedation, irritability, poor feeding, and extrapyramidal symptoms (tremors and abnormal muscle movements).

## 8.3 Females and Males of Reproductive Potential

### Infertility

#### Females

Based on the pharmacologic action of olanzapine (D<sub>2</sub> receptor antagonism), treatment with ZYPREXA RELPREVV may result in an increase in serum prolactin levels, which may lead to a reversible reduction in fertility in females of reproductive potential [see *Warnings and Precautions* (5.17)].

## 8.4 Pediatric Use

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

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 RELPREVV 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. In 5 placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis (n=1184), the following 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 greater with 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)]. 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, Dosage and Administration* (2.1), and *Warnings and Precautions* (5.3)].

## 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

ZYPREXA RELPREVV (olanzapine)

For Extended Release Injectable Suspension

dependence in rats administered oral doses up to 15 times the daily oral MRHD (20 mg) and rhesus monkeys administered oral doses up to 8 times the daily oral MRHD based on mg/m<sup>2</sup> body surface area.

Olanzapine has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. Because ZYPREXA RELPREVV 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 RELPREVV, 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 RELPREVV [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. The Specialty Distributor 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

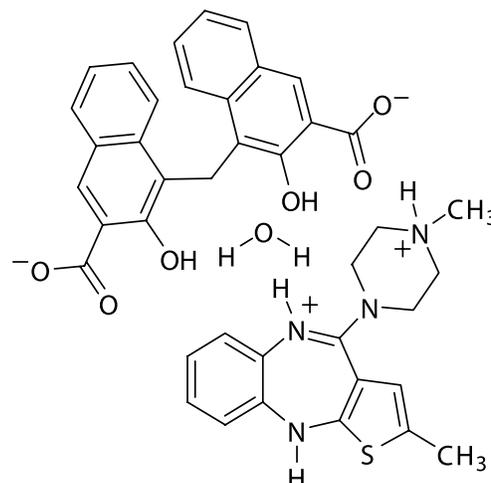
Post-injection delirium/sedation syndrome may occur with each injection of ZYPREXA RELPREVV. Signs and symptoms consistent with olanzapine overdose have been observed, and access to emergency response services must be readily available for safe use [see *Boxed Warning and Warnings and Precautions* (5.1)].

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.

## 11 DESCRIPTION

ZYPREXA RELPREVV 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 C<sub>17</sub>H<sub>22</sub>N<sub>4</sub>S•C<sub>23</sub>H<sub>14</sub>O<sub>6</sub>•H<sub>2</sub>O, which corresponds to a molecular weight of 718.8. The chemical structure is:



ZYPREXA RELPREVV (olanzapine)

For Extended Release Injectable Suspension

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

ZYPREXA RELPREVV includes a single-dose vial of the drug product and a vial of the sterile diluent for ZYPREXA RELPREVV.

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 RELPREVV 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 RELPREVV 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, in the listed indications is unclear. However, the efficacy of olanzapine in schizophrenia could be mediated through a combination of dopamine and serotonin type 2 (5HT<sub>2</sub>) antagonism.

### 12.2 Pharmacodynamics

Olanzapine binds with high affinity to the following receptors: serotonin 5HT<sub>2A/2C</sub>, 5HT<sub>6</sub> (K<sub>d</sub>=4, 11, and 5 nM, respectively), dopamine D<sub>1-4</sub> (K<sub>d</sub>=11-31 nM), histamine H<sub>1</sub> (K<sub>d</sub>=7 nM), and adrenergic α<sub>1</sub> receptors (K<sub>d</sub>=19 nM). Olanzapine is an antagonist with moderate affinity binding for serotonin 5HT<sub>3</sub> (K<sub>d</sub>=57 nM) and muscarinic M<sub>1-5</sub> (K<sub>d</sub>=73, 96, 132, 32, and 48 nM, respectively). Olanzapine binds with low affinity to GABA<sub>A</sub>, BZD, and β-adrenergic receptors (K<sub>d</sub>>10 μM).

### 12.3 Pharmacokinetics

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

Slow dissolution of ZYPREXA RELPREVV, a practically insoluble salt, after a deep intramuscular gluteal injection of a dose of ZYPREXA RELPREVV 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 RELPREVV 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 RELPREVV and orally administered olanzapine. The effective half-life for olanzapine after intramuscular ZYPREXA RELPREVV 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 RELPREVV 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 RELPREVV 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 RELPREVV corresponds to exposure for oral doses of olanzapine. A ZYPREXA RELPREVV dose of 300 mg olanzapine injected every two weeks delivers approximately 20 mg olanzapine per day and a ZYPREXA RELPREVV dose of 150 mg olanzapine injected every two weeks delivers approximately 10 mg per day. These ZYPREXA RELPREVV doses sustain steady-state olanzapine concentrations over long periods of treatment.

**Pharmacokinetic Impact of Switching to ZYPREXA RELPREVV from Oral Olanzapine** — The switch from oral olanzapine to ZYPREXA RELPREVV changes the pharmacokinetics from an elimination-rate-controlled to an absorption-rate-controlled process. The switch to ZYPREXA RELPREVV may require treatment for a period of approximately 3 months to re-establish steady-state conditions. Initial treatment with ZYPREXA RELPREVV 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<sub>1</sub>-acid glycoprotein.

**Metabolism and Elimination** — Following a single oral dose of <sup>14</sup>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 RELPREVV) 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 RELPREVV 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 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 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 RELPREVV 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 RELPREVV, 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 daily oral MRHD based on mg/m<sup>2</sup> body surface area) and 0.25, 2, 8 mg/kg/day (equivalent to 0.06-2 times the daily oral MRHD based on mg/m<sup>2</sup> body surface area). 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 daily oral MRHD based on mg/m<sup>2</sup> body surface area, respectively). The incidence of liver hemangiomas and hemangiosarcomas was significantly increased in 1 mouse study in female mice at 2 times the daily oral MRHD based on mg/m<sup>2</sup> body surface area. These tumors were not increased in another mouse study in females dosed up to 2-5 times the daily oral MRHD based on mg/m<sup>2</sup> body surface area; 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 daily oral MRHD based on mg/m<sup>2</sup> body surface area, respectively). Rats were also treated intramuscularly with ZYPREXA RELPREVV 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 daily oral MRHD of 300 mg every 2 weeks based on mg/m<sup>2</sup> body surface area; 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 RELPREVV control or pamoate 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 (1 and 1.5 times the daily oral MRHD based on mg/m<sup>2</sup> body surface area, respectively). Discontinuation of olanzapine treatment reversed the effects on male mating performance. In female rats, the precoital period was increased and the mating index reduced at 5 mg/kg/day (2.5 times the daily oral MRHD based

ZYPREXA RELPREVV (olanzapine)

For Extended Release Injectable Suspension

ZYPREXA RELPREVV (olanzapine)

For Extended Release Injectable Suspension

on mg/m<sup>2</sup> body surface area). Diestrus was prolonged and estrus delayed at 1.1 mg/kg/day (0.6 times the daily oral MRHD based on mg/m<sup>2</sup> body surface area); 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 daily oral MRHD based on mg/m<sup>2</sup> body surface area), 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 daily oral MRHD based on mg/m<sup>2</sup> body surface area) 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 daily oral MRHD based on mg/m<sup>2</sup> body surface area) for 3 months or 16 mg/kg (8 times the daily oral MRHD based on mg/m<sup>2</sup> body surface area) 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 RELPREVV 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 RELPREVV 210 mg every 2 weeks, ZYPREXA RELPREVV 405 mg every 4 weeks, ZYPREXA RELPREVV 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 RELPREVV (210 mg every 2 weeks, 405 mg every 4 weeks, and 300 mg every 2 weeks) as compared to placebo. The effectiveness of ZYPREXA RELPREVV 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 RELPREVV 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 RELPREVV 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 RELPREVV (45 mg every 4 weeks).

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

ZYPREXA RELPREVV convenience kit is supplied in single dose 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 RELPREVV 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 61269-660-20 — single-dose 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 61269-661-20 — single-dose 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 61269-662-20 — single-dose 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 RELPREVV should be stored at room temperature not to exceed 30°C (86°F). When the drug product is suspended in the solution for ZYPREXA RELPREVV, 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

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

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

### 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.

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

ZYPREXA RELPREVV (olanzapine)  
For Extended Release Injectable Suspension

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)].

### 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)].

### Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Patients should be advised to report to their health care provider at the earliest onset of any signs or symptoms that may be associated with Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) [see *Warnings and Precautions* (5.6)].

### Hyperglycemia and Diabetes Mellitus

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* (5.7)].

### Dyslipidemia

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

### 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* (5.7)].

### 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* (5.9) 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 heartbeat, or fainting.

### 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)].

### 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)].

### Concomitant Medication

Patients should be advised to inform their healthcare providers if they are taking, or plan to take, ZYPREXA or Symbyax® (olanzapine/fluoxetine combination). Patients should also be advised to inform their healthcare providers 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)].

### Alcohol

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

### Use in Specific Populations

**Pregnancy** — Advise women to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with ZYPREXA RELPREVV. Advise patients that ZYPREXA RELPREVV may cause extrapyramidal and/or withdrawal symptoms (agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder) in a neonate. Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ZYPREXA RELPREVV during pregnancy [see *Use in Specific Populations* (8.1)].

**Lactation** — Advise breastfeeding women using ZYPREXA RELPREVV to monitor infants for excess sedation, irritability, poor feeding and extrapyramidal symptoms (tremors and abnormal muscle movements) and to seek medical care if they notice these signs [see *Use in Specific Populations* (8.2)].

**Infertility** — Advise females of reproductive potential that ZYPREXA RELPREVV may impair fertility due to an increase in serum prolactin levels. The effects on fertility are reversible [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)].



Distributed by: H2-Pharma, LLC, Montgomery, AL 36117, USA

Licensed by: CHEPLAPHARM Registration GmbH, Weilerstr. 5e, 79540 Lörrach, Germany  
CHEPLAPHARM Registration GmbH under the license of CHEPLAPHARM Schweiz GmbH

ZYPREXA RELPREVV (olanzapine)  
For Extended Release Injectable Suspension

## 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.

ZYPREXA RELPREVV (olanzapine)  
For Extended Release Injectable Suspension

**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)

ZYPREXA RELPREVV (olanzapine)  
For Extended Release Injectable Suspension

- 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.
  - If you become pregnant while receiving ZYPREXA, talk to your healthcare provider about registering with the National Pregnancy Registry for Atypical Antipsychotics. You can register by calling 1-866-961-2388 or go to <http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/>.
- are breast-feeding or plan to breast-feed. ZYPREXA RELPREVV passes into your breast milk. 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
- **Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS):** DRESS can occur with ZYPREXA RELPREVV. Features of DRESS may include rash, fever, swollen glands and other internal organ involvement such as liver, kidney, lung and heart. DRESS is sometimes fatal; therefore, tell your doctor immediately if you experience any of these signs.
- **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 1-866-770-9010 or visit [www.zyprexarelpbev.com](http://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 October, 2023



Distributed by: **H2-Pharma, LLC**  
Montgomery, AL 36117, USA

Licensed by: **CHEPLAPHARM Registration GmbH**  
Weilerstr. 5e, 79540 Lörrach, Germany

**[www.zyprexarelpbev.com](http://www.zyprexarelpbev.com)**

CHEPLAPHARM Registration GmbH under the license  
of CHEPLAPHARM Schweiz GmbH

PP-OD-US-0080

ZYPREXA RELPREVV (olanzapine)  
For Extended Release Injectable Suspension