ZYPREXA RELPREVV

(olanzapine) For Extended Release Injectable Suspension

Training for Healthcare Professionals

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

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

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

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ZYPREXA RELPREVV: Indication

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

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

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

Version 2.0 03-Aug-2012

ZYPREXA Relprevv (olanzapine) For Extended Release Injectable Suspension

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

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

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ZYPREXA RELPREVV: Boxed Warnings

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

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

Version 2.0 03-Aug-2012

Zyprexa Relprevv (olanzapine) For Extended Release Injectable Suspension

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

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

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Training Content

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

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

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

Version 2.0 03-Aug-2012

ZYPREXA Relprevv (olanzapine) For Extended Release Injectable Suspension

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

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

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ZYPREXA RELPREVV and ZYPREXA IntraMuscular –

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

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

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

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ZYPREXA Relprevv (olanzapine) For Extended Release Injectable Suspension

ZYPREXA IntraMuscular Olanzapine for Injection

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

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

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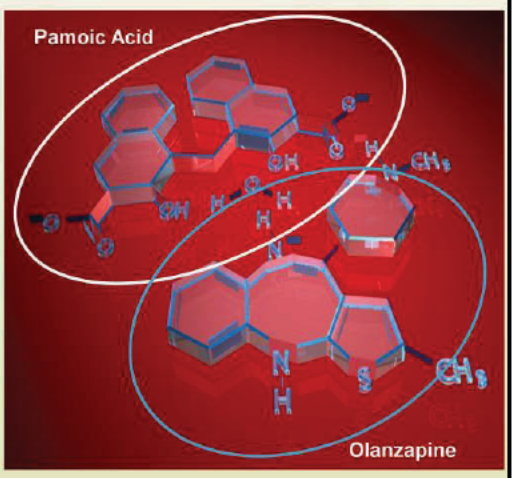
ZYPREXA RELPREVV: Formulation

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



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Zyprexa Relprevv (olanzapine) For Extended Release Injectable Suspension

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

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

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ZYPREXA RELPREVV: Product Characteristics

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

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

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

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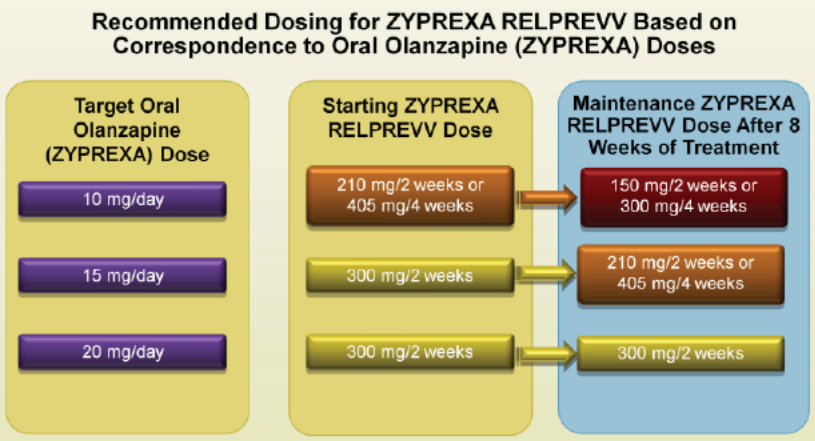
ZYPREXA Relprevv (olanzapine) For Extended Release Injectable Suspension

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

Dosing of ZYPREXA RELPREVV



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ZYPREXA Olanzapine

ZYPREXA Relprevv (olanzapine) For Extended Release Injectable Suspension

Transition

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

Key points

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

Reference ID: 4596482

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

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

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

None of these events were statistically significantly different

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

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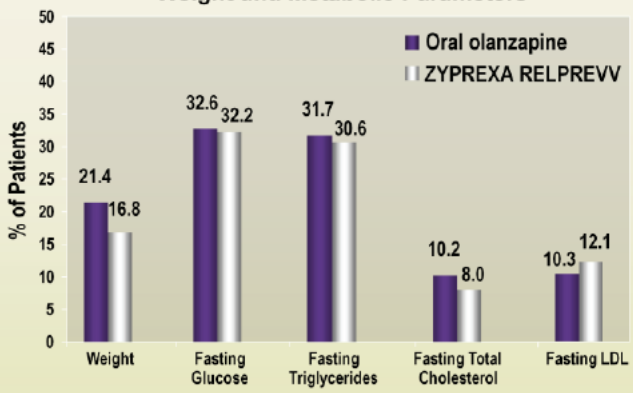
ZYPREXA Relprevv (olanzapine) For Extended Release Injectable Suspension

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

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



- No significant differences between groups

		Weight	Fasting Glucose	Fasting Triglycerides	Fasting Total Cholesterol	Fasting LDL
Oral olanzapine	N	322	285	265	265	253
ZYPREXA RELPREVV	N	595	481	448	448	429

Potentially clinically significant definitions: weight, ≥7% change from baseline; fasting glucose, ≥10 mg/dL increase; fasting triglycerides, ≥50 mg/dL increase; total fasting cholesterol, ≥40 mg/dL increase; fasting LDL, ≥30 mg/dL increase.
Data on file, Lilly Research Laboratories; ZYP20081112A.

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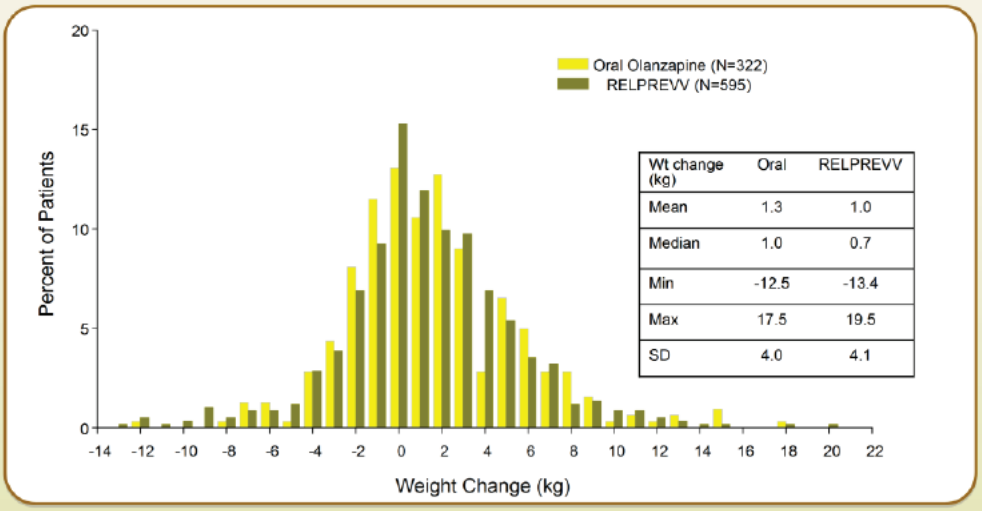
ZYPREXA Relprevv (olanzapine) For Extended Release Injectable Suspension

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

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

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



Wt change (kg)	Oral	RELPREVV
Mean	1.3	1.0
Median	1.0	0.7
Min	-12.5	-13.4
Max	17.5	19.5
SD	4.0	4.1

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

Oral = Oral olanzapine.

Data on file, Lilly Research Laboratories, ZYP20081112D

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ZYPREXA Relprevv (olanzapine) For Extended Release Injectable Suspension

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

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Differences by Dose with ZYPREXA RELPREVV

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

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

[a] Mean change
[b] Change from normal at baseline to high at any time (%)

*$P<.05$ versus 150 mg/2 wk
†$P<.05$ versus 405 mg/4 wk

Data on file, Lilly Research Laboratories, ZYP20081112B

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ZYPREXA Relprevv (olanzapine) For Extended Release Injectable Suspension

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

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Metabolic Monitoring

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

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

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ZYPREXA Relprevv (olanzapine) For Extended Release Injectable Suspension

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

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Metabolic Monitoring

- **Hyperlipidemia**
  - Undesirable lipid alterations have been observed. Clinical monitoring including baseline and follow-up lipid evaluations is advised
  - Clinically significant, sometimes very high, elevations in triglycerides and modest mean increases in total cholesterol have been observed with olanzapine use
- **Weight**
  - Monitor patient weight regularly during treatment with olanzapine
  - Consider potential consequences of weight gain prior to initiating olanzapine

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

Version 2.0 03-Aug-2012

Zyprexa Relprevv (olanzapine) For Extended Release Injectable Suspension

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

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

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

A PDSS event can occur in any patient at any injection

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

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

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Zyprexa Relprevv (olanzapine) For Extended Release Injectable Suspension

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

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

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

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What is Post-Injection Delirium/Sedation Syndrome?

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

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

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

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Version: 2.0 03-Aug-2012

ZYPREXA Relprevv (olanzapine) For Extended Release Injectable Suspension

What is Post-injection Delirium/Sedation Syndrome?

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

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Medical Status and Recovery

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

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

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ZYPREXA Relprevv (olanzapine) For Extended Release Injectable Suspension

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

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

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Safety Precautions at Every ZYPREXA RELPREVV Injection

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

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

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ZYPREXA Relprevv (olanzapine) For Extended Release Injectable Suspension

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

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

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

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Safety Precautions at Every ZYPREXA RELPREVV Injection

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

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

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ZYPREXA Relprevv (olanzapine) For Extended Release Injectable Suspension

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

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

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

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Safety Precautions at Every ZYPREXA RELPREVV Injection

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

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ZYPREXA Relprevv (olanzapine) For Extended Release Injectable Suspension

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

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Safety Precautions at Every ZYPREXA RELPREVV Injection

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

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ZYPREXA Relprevv (olanzapine) For Extended Release Injectable Suspension

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

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

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

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Clinical Management of PDSS Events

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

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

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ZYPREXA Relprevv (olanzapine) For Extended Release Injectable Suspension

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

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

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Clinical Management Following PDSS Events

Following a PDSS event

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

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ZYPREXA Relprevv (olanzapine) For Extended Release Injectable Suspension

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

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

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

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ZYPREXA RELPREVV Patient Care Program

- **ZYPREXA RELPREVV is available only through a controlled distribution system to registered prescribers for use in registered facilities**
- **The goal of the ZYPREXA RELPREVV Patient Care Program is to mitigate the risk of negative outcomes associated with ZYPREXA RELPREVV post-injection delirium/sedation syndrome (PDSS) by:**
  - Ensuring ZYPREXA RELPREVV is prescribed only by certified prescribers, dispensed only by certified dispensers, and dispensed for use only in certified healthcare facilities with ready access to emergency response services, and dispensed for use only with documentation of safe use conditions;
  - Informing health care providers and patients about the risks and the need for continuous observation of patients for at least 3 hours in certified healthcare facilities; and
  - Establishing long-term safety and safe use of ZYPREXA RELPREVV through periodic monitoring for the risk of PDSS events and by enrolling all patients who receive ZYPREXA RELPREVV in the ZYPREXA RELPREVV Patient Care Program registry.

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ZYPREXA Relprevv (olanzapine) For Extended Release Injectable Suspension

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

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

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

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Required Enrollments

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

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

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ZYPREXA Relprevv (olanzapine) For Extended Release Injectable Suspension

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

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

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

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Prescriber Registration

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

- **Prescriber obligations include:**
  - Completing the mandatory ZYPREXA RELPREVV training
  - Understanding the ZYPREXA RELPREVV Patient Care Program requirements and the risks associated with ZYPREXA RELPREVV
  - Understanding the clinical presentation of PDSS and how to manage patients should an event occur while using ZYPREXA RELPREVV
  - Understanding that ZYPREXA RELPREVV should only be administered to patients in healthcare settings (e.g., hospitals, clinics) that have ready access to emergency response services and that can allow for continuous patient monitoring for at least 3 hours post-injection
  - Initiating ZYPREXA RELPREVV only in patients for whom tolerability with oral olanzapine has been established
  - Reviewing the ZYPREXA RELPREVV Medication Guide with each patient or legal guardian prior to prescribing
  - Ensuring that all patients are enrolled in the ZYPREXA RELPREVV Patient Care Program registry prior to prescribing ZYPREXA RELPREVV by completing the Patient Registration Form
  - Ensuring all suspected cases of PDSS are reported to the ZYPREXA RELPREVV Patient Care Program within 24 hours of becoming aware of the event
  - Agreeing to be contacted by the ZYPREXA RELPREVV Patient Care Program coordinating center to resolve discrepancies, to obtain information about a patient, or to conduct occasional surveys

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ZYPREXA Relprevv (olanzapine) For Extended Release Injectable Suspension

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

Prescriber obligations include:

- Completing the mandatory ZYPREXA RELPREVV training
- Understanding the ZYPREXA RELPREVV Patient Care Program requirements and the risks associated with ZYPREXA RELPREVV
- Understanding the clinical presentation of PDSS and how to manage patients should an event occur while using ZYPREXA RELPREVV
- Understanding that ZYPREXA RELPREVV should only be administered to patients in healthcare settings (e.g., hospitals, clinics) that have ready access to emergency response services and that can allow for continuous patient monitoring for at least 3 hours post-injection
- Initiating ZYPREXA RELPREVV only in patients for whom tolerability with oral olanzapine has been established
- Reviewing the ZYPREXA RELPREVV Medication Guide with each patient or legal guardian prior to prescribing
- Ensuring that all patients are enrolled in the ZYPREXA RELPREVV Patient Care Program registry prior to prescribing ZYPREXA RELPREVV by completing the Patient Registration Form
- Ensuring all suspected cases of PDSS are reported to the ZYPREXA RELPREVV Patient Care Program within 24 hours of becoming aware of the event
- Agreeing to be contacted by the ZYPREXA RELPREVV Patient Care Program coordinating center to resolve discrepancies, to obtain information about a patient, or to conduct occasional surveys

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Patient Registration

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

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

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Zyprexa Relprevv (olanzapine) For Extended Release Injectable Suspension

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

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

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Healthcare Facility or Program Registration

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

- **Healthcare facility obligations include:**
  - Ensuring that all appropriate staff are trained and have read and understand the ZYPREXA RELPREVV Patient Care Program Instructions Brochure as well as the Training Materials
  - Ensuring that all appropriate staff understand that ZYPREXA RELPREVV can only be dispensed for use in certain health care settings (e.g., hospitals, clinics) that have ready access to emergency response services that can allow for continuous patient monitoring for at least 3 hours post-injection
  - Ensuring the facility has systems, protocols, or other measures to ensure that ZYPREXA RELPREVV is only administered to patients enrolled in the program, and that patients are continuously monitored for at least 3 hours post-injection for suspected PDSS
  - Ensuring that appropriate staff will verify that the patient is enrolled in the ZYPREXA RELPREVV Patient Care Program registry prior to each injection by accessing the system
  - Ensuring that the Medication Guide is provided to the patient or legal guardian prior to each injection
  - Ensuring that the appropriate staff monitors the patient continuously for at least 3 hours
  - Ensuring that required data are submitted within 7 days after each injection to the ZYPREXA RELPREVV Patient Care Program
  - Understanding the facility may be contacted by the ZYPREXA RELPREVV Patient Care Program Coordinating Center to clarify information provided or obtain information about the patient

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ZYPREXA Relprevv (olanzapine) For Extended Release Injectable Suspension

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

Healthcare facility obligations include:

- Ensuring that all appropriate staff are trained and have read and understand the ZYPREXA RELPREVV Patient Care Program Instructions Brochure as well as the Training Materials
- Ensuring that all appropriate staff understand that ZYPREXA RELPREVV can only be dispensed for use in certain health care settings (e.g., hospitals, clinics) that have ready access to emergency response services that can allow for continuous patient monitoring for at least 3 hours post-injection
- Ensuring the facility has systems, protocols, or other measures to ensure that ZYPREXA RELPREVV is only administered to patients enrolled in the program, and that patients are continuously monitored for at least 3 hours post-injection for suspected PDSS
- Ensuring that appropriate staff will verify that the patient is enrolled in the ZYPREXA RELPREVV Patient Care Program registry prior to each injection by accessing the system
- Ensuring that the Medication Guide is provided to the patient or legal guardian prior to each injection
- Ensuring that the appropriate staff monitors the patient continuously for at least 3 hours
- Ensuring that required data are submitted within 7 days after each injection to the ZYPREXA RELPREVV Patient Care Program
- Understanding the facility may be contacted by the ZYPREXA RELPREVV Patient Care Program Coordinating Center to clarify information provided or obtain information about the patient

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Pharmacy Service Provider Registration

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

- **Pharmacy Service Provider obligations include:**
  - Ensuring that all appropriate pharmacy staff are trained and have read and understand the ZYPREXA RELPREVV Patient Care Program Instructions Brochure
  - Ensuring that all appropriate pharmacy staff understand that ZYPREXA RELPREVV can only be dispensed for use in certain health care settings (e.g., hospitals, clinics) that have ready access to emergency response services that can allow for continuous patient monitoring for at least 3 hours post-injection
  - Ensuring that pharmacy staff will verify that the patient is enrolled in the ZYPREXA RELPREVV Patient Care Program registry prior to dispensing each prescription/refill by accessing the system
  - Ensuring that pharmacy staff will not dispense ZYPREXA RELPREVV directly to patients
  - Ensuring that pharmacy staff report the date of each ZYPREXA RELPREVV dispensing to the ZYPREXA RELPREVV Patient Care Program
  - Understanding that the pharmacy may be contacted by the ZYPREXA RELPREVV Patient Care Program to clarify information provided or to obtain information about a patient

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ZYPREXA Relprevv (olanzapine) For Extended Release Injectable Suspension

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

Pharmacy Service Provider obligations include:

•Ensuring that all appropriate pharmacy staff are trained and have read and understand the ZYPREXA RELPREVV Patient Care Program Instructions Brochure

•Ensuring that all appropriate pharmacy staff understand that ZYPREXA RELPREVV can only be dispensed for use in certain health care settings (e.g., hospitals, clinics) that have ready access to emergency response services that can allow for continuous patient monitoring for at least 3 hours post-injection

•Ensuring that pharmacy staff will verify that the patient is enrolled in the ZYPREXA RELPREVV Patient Care Program registry prior to dispensing each prescription/refill by accessing the system

•Ensuring that pharmacy staff will not dispense ZYPREXA RELPREVV directly to patients

•Ensuring that pharmacy staff report the date of each ZYPREXA RELPREVV dispensing to the ZYPREXA RELPREVV Patient Care Program

•Understanding that the pharmacy may be contacted by the ZYPREXA RELPREVV Patient Care Program to clarify information provided or to obtain information about a patient

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Training Summary

After this training, you should now be able to:

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

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ZYPREXA Relprevv (olanzapine) For Extended Release Injectable Suspension

After this training, you should now be able to:

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