

# Demystifying Zyprexa Relprevv usage

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## ABSTRACT

Zyprexa Relprevv, an extended-release injectable suspension of olanzapine, received FDA approval in December 2009 for the treatment of schizophrenia in adults. Due to the risk of post-injection delirium/sedation syndrome (PDSS) associated with Zyprexa Relprevv usage, the injection is only available through a restricted distribution program. This article reviews the impact of PDSS on the use of Zyprexa Relprevv.

## KEYWORDS

Zyprexa Relprevv, olanzapine, long-acting injectable, antipsychotic, depot

Zyprexa Relprevv, an extended-release injectable suspension of olanzapine, received FDA approval in December 2009 for the treatment of schizophrenia in adults.<sup>1</sup> Zyprexa Relprevv can be administered once every two to four weeks, depending on the patient's target oral olanzapine dose. Due to the risk of post-injection delirium/sedation syndrome (PDSS) associated with Zyprexa Relprevv usage, the injection is only available through a restricted distribution program, requiring enrollment by the healthcare facility administering the injection, as well as the patient, prescriber, and pharmacy dispensing the injection. Though PDSS is rare and has occurred in less than 0.1 % of injections and in approximately 2% of patients who received injections up to 46 months, it is still an alarming adverse effect that warrants careful administration and monitoring.

The occurrence of PDSS has been associated with an unpredictable rapid attainment of supra-therapeutic plasma concentrations of olanzapine. Approximately 80% of PDSS cases have developed within one hour of receiving the injection, while <1/1000 injections and <1/10,000 injections have resulted in PDSS one to three hours and greater than three hours post-injection, respectively. The exact mechanism describing the rapid entrance of olanzapine into the circulation is unknown, since it is a deep intramuscular gluteal injection designed to provide slow-release, rate-controlled absorption of olanzapine. Manufacturing irregularities, improper drug reconstitution, and inappropriate dosing have been excluded as possible causes, and instead PDSS is thought to result from accidental partial intravascular injection or

blood vessel injury during injection causing olanzapine to enter into the circulation.<sup>2</sup>

Because of the risk of PDSS, Zyprexa Relprevv cannot be dispensed directly to the patient and can only be administered in a registered healthcare facility with immediate access to emergency services.<sup>1</sup> Additionally, patients must be observed for symptoms similar to an olanzapine overdose, including sedation and/or delirium (e.g., confusion, disorientation, agitation, anxiety) by a healthcare professional for a minimum of 3 hours post-injection. Before the patient can be released, the healthcare professional must confirm the patient is alert, oriented, and absent of signs and symptoms consistent with PDSS. Patients must also be accompanied to their final destination upon leaving the facility. Because of the complicated logistics surrounding the use of Zyprexa Relprevv, I was curious to learn what type of facilities were administering this injection and the experience of members who have used or attempted to use Zyprexa Relprevv in their patients.

In a survey included in the November issue of the *Mental Health Clinician*, six CPNP members stated they had difficulty dedicating a staff member to observe the patient for a minimum of 3 hours post-injection. Four members endorsed the injection was too expensive for their facility, while one member stated they had a patient receiving Zyprexa Relprevv who either decompensated or required oral supplementation in addition to the injection. Another member claimed their facility had difficulty getting their staff trained. Two members confirmed that they had encountered no barriers to usage.

**Table 1. CPNP Members' Experiences with Zyprexa Relprevv (Formulary Approved / Pending Formulary Approval)**

Facility	Formulary Information	# Patients on Relprevv	Training/ Staffing	Cost/ Reimbursement	Successes/ Failures	Special Notes
<b>State Hospital Kanohe, Hawaii</b>	-In the formulary approval process -Rate-limiting step to obtaining formulary approval is finding outpatient prescribers to continue injection in the community	-6	-Staffing/training not an issue -Lilly rep has helped with training process	-No issues	-Symptom improvement in 3 patients: all appeared stable, goal-oriented and less distracted -1 patient scheduled to receive injection never got it b/c unable to verify pt could be maintained on injection post- discharge -1 patient discharged on injection but had it discontinued as an outpatient; pt decompensated and was re-admitted to hospital; pt was reluctant to be reinitiated on injection so it was not restarted -1 patient was switched to clozapine b/c of non-response to injection	-Takes a few days to receive injection via drop shipment
<b>Inpatient psychiatric unit and affiliated outpatient community clinic  Indianapolis, IN</b>	-On formulary b/c oral olanzapine shown to be effective	-1 inpatient -3 outpatient	-Lilly rep provided inservice to all staff	-Issues with getting insurance company to pay for injection b/c either non-formulary or prior-authorization required	-No information provided	-Pharmacist created referral form for physicians to prevent inappropriate starts and monitoring form to assist with PDSS monitoring -When transitioning pt from inpatient to outpatient setting, new registration required and pt signature needed again
<b>State supported living center for mental impairment and developmentally disabled  Lufkin, TX</b>	-On formulary with restrictions -Requires written approval of hospital director and local mental health clinic director prior to initiation of therapy	-Information not provided	-Information not provided	-Not an issue	-One patient was refusing to take oral olanzapine and was switched to injection- no further information provided	---
<b>State Hospital  San Antonio, TX</b>	-On formulary with restrictions -Requires written approval from outpatient clinic verifying pt can continue injection upon discharge	-Information not provided	---	---	---	---

Abbreviations:  
Pt(s): patient(s)  
PDSS: Post-Injection Delirium/Sedation Syndrome  
BBW: Black Box Warning

**Table 2. CPNP Members' Experiences with Zyprexa Relprevv (Non-Formulary)**

Facility	Formulary Information	# Patients on Relprevv	Training/ Staffing	Cost/ Reimbursement	Successes/ Failures	Special Notes
<b>Free standing psychiatric hospital</b> <b>Los Angeles, CA</b>	-Information not provided	-0	-Information not provided	-Encountered much difficulty when attempting to get reimbursed from Lilly for returning drug	-1 pt was going to be initiated on injection but encountered difficulty when trying to find registered outpatient clinic b/c most do not have required safety features; patient was then switched to different depot antipsychotic	---
<b>Inpatient psychiatric unit at a non-profit community hospital</b> <b>Southwest Georgia</b>	-Not on formulary	-8 to 9	-All nurses on unit trained; Lilly rep helped train nurses -Pts monitored on unit and undergo q 15 min checks	-Only patients on Medicaid have received injection thus far; no reimbursement issues for Medicaid pts	-No adverse events experienced	-Pharmacist verifies outpatient clinic and provider are registered prior to ordering injection -Injection received in 24 to 48 hours
<b>Inpatient psychiatric hospital</b> <b>Las Vegas, New Mexico</b>	-Not on formulary	-0	-Do not have staff available for monitoring	-Most pts under Medicare/Medicaid and payors do not cover it	---	---
<b>Inpatient hospital</b> <b>Oklahoma City, OK</b>	-Not on formulary because of "its problems"	-0	---	---	---	---
<b>Free -standing psychiatric hospital</b> <b>Johnson City, TN</b>	-Not on formulary	-2 to 3	-Not an issue but did cause a delay in the obtainment and subsequent administration of injection	-High cost factored into decision to make non-formulary -Hospital paid the same rate per patient regardless of amount spent or charged	-Injection did not appear to provide benefit for the few treatment-resistant patients receiving injection	---
<b>County Jail</b> <b>Dallas, TX</b>	-Not on formulary but may be added for patients transferred to county jail from state hospital and already on injection -Had one pt return to jail from state hospital who was unable to continue injection b/c jail was not registered site	-0	---	---	---	---
<b>Outpatient VA Psychiatric Clinic</b> <b>San Antonio, TX</b>	-Not on formulary -Pharmacy and physicians reluctant to register	-0	-Nurses unavailable to monitor patients	---	---	---
<b>Inpatient psychiatric unit</b> <b>San Antonio, TX</b>	-Not on formulary -Not many outpatient clinics administer injection -Cumbersome to register pharmacy, patient, and provider	-0	---	-High cost factored into decision to make non-formulary	---	---

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Facility	Formulary Information	# Patients on Relprevv	Training/ Staffing	Cost/ Reimbursement	Successes/ Failures	Special Notes
<b>Inpatient psychiatric unit of academic medical center</b> <b>San Antonio, TX</b>	-Not on formulary -Long-acting injections thought to be more appropriate for outpatient use due to inpatient cost/reimbursement issues	-0	---	-High cost factored into decision to make non-formulary	---	
<b>Inpatient psychiatric unit of academic medical center</b> <b>Richmond, VA</b>	-Not on formulary -Most outpatient clinics and psychiatrists are not using injection -PO formulation just as effective -All other injectables currently on formulary	-0	-Cumbersome	---	---	---
<b>Independent Mental Health Pharmacy</b> <b>Spokane, WA</b>	-Registered as pharmacy to dispense drug but pharmacist must go to community triage center to administer drug since pharmacy is not set-up for monitoring pts for 3 hours post-injection and clinic nurses not comfortable administering injection, despite undergoing training	-3	---	-No issues but are not getting reimbursed for administration	-3 pts on Relprevv; 1 pt taking oral Zyprexa prn and other 2 pts undergoing intensive case management - All noted to be doing well	-Located on West Coast, so experience difficulty with ordering med due to time difference - “Drop shipment” or “next day delivery” typically means 2-3 business days
<b>State Hospital</b> <b>Tacoma, WA</b>	-Not on formulary -BBW factored into decision to make non-formulary	-0	-3 hour monitoring and ongoing paperwork also factored into decision to make non-formulary	-High cost also factored into decision to make non-formulary	---	---

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Pt(s): patient(s)

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Tables 1 and 2 were compiled from information provided by CPNP members on their experiences with Zyprexa Relprevv. Of the 16 members who responded to an email inquiry through the list serve requesting information about their experiences, twelve responses (75%) were provided by clinicians (or administrators) practicing in an inpatient psychiatric unit or at a psychiatric hospital, while one response was received from clinicians at each of the following practice sites: a county jail, a state-supported living center for mentally-ill/disabled patients, an outpatient clinic, an independent psychiatric pharmacy, and an inpatient psychiatric unit affiliated with an outpatient psychiatric clinic. One inpatient psychiatric unit, one state hospital, and one state-supported living center have added Zyprexa Relprevv to their formularies; however, two of these facilities have imposed restrictions on its use. An additional state hospital is currently in the process of obtaining formulary approval for the injection but is experiencing delays due to a lack of outpatient clinics registered to dispense and administer the injection. Seventy-five percent (9/12) of inpatient psychiatry units and psychiatric hospitals have not added Zyprexa Relprevv to their formulary. Barriers to Zyprexa Relprevv usage identified by members responding to the email inquiry include: a) the high cost of the injection and/or reimbursement issues (44%; 7 members), b) a lack of registered outpatient clinics (25%; 4 members), and c) limited staff availability for required monitoring (19%; 3 members). It appears facilities administering the injection have had Eli Lilly drug representatives provide training to their staff with much success (3 members). Based on the information provided by 16 members, up to 25 patients have been initiated on Zyprexa Relprevv. Though many members did not or were unable to provide information on the efficacy and/or tolerability of the injection, 6 patients were stated to be doing well on the injection, while about 4 patients were described as not deriving benefit from the injection. To optimize Zyprexa Relprevv usage, Kelly Williams, a Clinical Pharmacy Specialist at Wishard Health Services/Midtown Community Mental Health Center has developed a [prescriber referral form](#) to prevent patients from being inappropriately initiated on Zyprexa Relprevv. She also created an [observation form](#) to assist with monitoring for PDSS. Overall, if cost and/or reimbursement issues are surmounted, the facilities are well-staffed, and all involved entities (i.e., pharmacy, provider, facility administering the injection, patient) have registered with the Zyprexa Relprevv program, it appears the injection may be a viable option for those responding to the oral formulation of Zyprexa but with medication adherence issues; however, it should be noted

that long-acting injectables do not guarantee adherence and patients stabilized on 20 mg/day of oral Zyprexa will require an injection once every two weeks rather than monthly.

## REFERENCES

1. Zyprexa Relprevv [package insert]. Eli Lilly and Company, Indianapolis, IN. July 2011. [http://pi.lilly.com/us/zyprexa\\_relprevv.pdf](http://pi.lilly.com/us/zyprexa_relprevv.pdf). Accessed November 30, 2011.
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