

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-173**

**SUMMARY REVIEW**

**MEMORANDUM****DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**DATE:** 11 December 2009

**FROM:** Mitchell V. Mathis, M.D.  
Deputy Director  
Division of Psychiatry Products, HFD-130

**TO:** File NDA 22-173, first submitted 30 April 2007

**SUBJECT:** Zyprexa Relprevv (olanzapine pamoate) for Extended Release Injectable Suspension for the Treatment of Schizophrenia; Approval Recommendation

Zyprexa is an atypical antipsychotic (5HT<sub>2</sub> and D<sub>2</sub> antagonist) approved for schizophrenia and bipolar disorder. This application is for a long-acting injectable form of Zyprexa given every two to four weeks. The intended use for this product is the same as other extended release injectable antipsychotics—as an alternative to taking oral medications in patients with schizophrenia. This is a useful option for clinicians because it offers a way to ensure compliance, and it increases convenience for some patients.

This application was reviewed by the Division prior to the first goal date and the drug was found to be effective (see earlier reviews by Drs. Zhang and Laughren). Our primary concern, and the reason for our having issued a Complete Response (CR) letter, was safety. The safety of Zyprexa oral is well documented and risks to patients are identified in labeling; the safety profile of this long-acting injectable is similar to the oral formulation except for two adverse events: injection site pain, and post-injection delirium/sedation syndrome (PDSS).

Post-injection pain is expected with this injectable suspension, as it is with other injectable products, but PDSS is a safety issue not seen with other long-acting injectable antipsychotics. PDSS events are characterized by severe CNS depression (sometimes requiring resuscitative intervention) that is consistent with symptoms seen with olanzapine overdose. Despite our best efforts to understand these events, including taking this application to the PDAC, we still cannot explain with certainty why some patients suffer these events with certain injections (but not most injections) and others do not. It appears that there are higher than expected blood levels of olanzapine in many of these cases of PDSS, but the clinical consequences do not always correlate with blood concentrations. It was thought at one time that PDSS events were due to inadvertent intravascular injection, yet the events have happened as late as five hours after injection (most within one hour), and re-training of nursing staff at the clinical study sites on proper injection technique did not change the rate of PDSS events. The risk for PDSS events seems to be present with each injection, and so patients must be monitored after each injection. PDSS occurs infrequently, but is potentially severe, and so in our CR letter we required the sponsor to develop a risk evaluation and mitigation strategy (REMS) to specifically address safe prescription parameters.

The sponsor responded to our CR Letter with a REMS that includes a Medication Guide and a program to ensure the safe use of the drug in clinical practice. We worked with OSE safety reviewers to modify the REMS and the label and have negotiated our changes with the sponsor. We believe that labeling and the REMS together now provide for the safe use of Zyprexa Relprevv.

### REMS

Although the risk of PDSS is small with any single injection (estimated to be about 0.07%), the consequences of severe CNS depression are significant, and the risk is cumulative in the sense that it is present with every injection, and patients will receive injections every two or four weeks. Therefore, the risk mitigation strategy focuses on ensuring that patients are observed for at least three hours after each injection for signs of CNS depression in a facility with access to emergency medical services. The details of how this will be accomplished can be found in OSE's review, but they include requirements for prescriber training and registration, as well as training and registration for the staff of certified facilities on how to minimize the risk of PDSS events and respond to them when they occur.

The Medication Guide alerts caregivers to the possibility of PDSS events and characterizes them in lay language so that patients may continue to be monitored by caregivers after they leave the injection facility. Patients are required to be escorted from the facility after each injection and are instructed not to operate heavy machinery for 24 hours after each injection.

The REMS also includes reporting and database maintenance requirements which will keep the division informed of these serious ARs and allow us to more accurately assess this risk after the drug has been marketed.

### LABELING

We have written labeling to be consistent with the REMS. The Boxed Warning and Warnings and Precautions sections of labeling have been expanded to include the REMS-required training and distribution requirements (must not be dispensed directly to the patient), and it is clear from the Warnings and Precautions section that these events are potentially severe, that the risk is present with each injection, and that there are strict registration and monitoring requirements that must be satisfied before the drug can be administered.

### RESOLUTION OF OUTSTANDING ISSUES

There were two final concerns resolved as part of this review cycle: CMC had asked that "pamoate" not be included as part of the approved name, and OCP had made an argument for loading doses to be consistent across dosing regimens regardless of patient's stable dose of oral olanzapine prior to switching to Relprevv.

Regarding the approved name: CMC had argued that since olanzapine pamoate is a salt and the different strengths of the active drug do not include the weight of the salt, "pamoate" should be dropped from the name to avoid confusion. DMEPA and Lilly agreed with this change and so the name was finalized to ZYPREXA RELPREVV (olanzapine) For Extended Release Injectable Suspension.

Regarding the loading dose: OCP had argued that, based upon simulation data, patients switched from different oral doses of olanzapine to RELPREVV should all be given the same eight weeks of loading with RELPREVV (300 mg every two weeks). The sponsor agreed that this loading scheme would be appropriate for patients stable on 15 mg/day or 20 mg/day of oral olanzapine, but they asked that a more conservative approach be taken for patients stable on 10 mg/day. This issue was discussed with OCP and we agreed with the sponsor that the loading dose for patients stable on the smaller dose of oral olanzapine (10 mg/day) should be less than other patients, and this is reflected in labeling.

## **Conclusions and Recommendations**

There has been no disagreement about the efficacy data submitted to support this application. We believe the drug is effective, and we know the oral formulation is effective.

There has been a great deal of discussion and consultation with OSE to determine the best way to monitor for PDSS events. Since these events are expected to continue to occur after the drug is marketed, and since we have no clear understanding of the mechanism involved in producing these events, our focus has been on implementing a REMS and labeling that require the education of patient care staff and other caregivers about the possibility of PDSS, and on restricting the use of the drug to registered patients by registered clinicians in registered facilities. We have decided that the registration process, the distribution restrictions, the provider training, the three hour monitoring requirement, along with the Medication Guide, and the requirement that patients be escorted after each injection adequately provide for patient safety. With the REMS in place, we will have the ability to reassess the effectiveness of our safety monitoring procedures and to adjust them in the future if the data indicate that we should do so to further protect patients.

I agree with the review team that the sponsor has submitted sufficient data to support the conclusion that Zyprexa Relprevv is effective for the treatment of schizophrenia. I also believe that the REMS and labeling we have negotiated with the sponsor in concert with OSE allow for the safe use of the product, and so I would recommend that the Director approve this application.



Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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NDA-22173	ORIG-1	ELI LILLY CO	ZYPREXA/ADHERA

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/s/

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MITCHELL V Mathis  
12/11/2009