



### **FDA Drug Safety Communication: FDA review of study sheds light on two deaths associated with the injectable schizophrenia drug Zyprexa Relprevv (olanzapine pamoate)**

This is an update to the FDA Drug Safety Communication: FDA is Investigating Two Deaths Following Injection of Long-Acting Antipsychotic Zyprexa Relprevv (Olanzapine Pamoate) issued on [June 18, 2013](#).

#### **Safety Announcement**

**[03-23-2015]** The U.S. Food and Drug Administration (FDA) has concluded a review of a study undertaken to determine the cause of elevated levels of the injectable schizophrenia drug Zyprexa Relprevv (olanzapine pamoate) in two patients who died. The study results were inconclusive. We are unable to exclude the possibility that the deaths were caused by rapid, but delayed, entry of the drug into the bloodstream following intramuscular injection. The study suggested that much of the drug level increase could have occurred after death, a finding that could explain the extremely high blood levels found in the two patients who died 3 to 4 days after receiving injections of appropriate doses of Zyprexa Relprevv. On the basis of all of the information reviewed, we are not recommending any changes to the current prescribing or use of Zyprexa Relprevv injection at this time. Patients should not stop receiving treatment without first talking to their health care professionals.

Treatment with Zyprexa Relprevv may help improve the symptoms of schizophrenia, which include hearing voices, seeing things that are not there, and being suspicious or withdrawn. The labeling for Zyprexa Relprevv carries a boxed warning, FDA's most serious type of warning, for post-injection delirium sedation (PDSS). PDSS is a serious condition with signs and symptoms consistent with olanzapine overdose, in particular, sedation (including coma), delirium, or both. In clinical trials, cases of PDSS were observed within 3 hours after giving an intramuscular injection of Zyprexa Relprevv, although no deaths were reported. To reduce the risk of PDSS, there is also a Risk Evaluation and Mitigation Strategy (REMS) for Zyprexa Relprevv to ensure that patients are observed by health care professionals at a certified facility following injection.

Following the deaths of the two patients who received appropriate doses of Zyprexa Relprevv, FDA requested the drug's manufacturer, Eli Lilly and Company, to conduct an animal study to test whether movement of olanzapine into blood after death could lead to higher-than-expected blood levels of the drug. The study showed that some animals had increases in drug levels in the blood after death, which could account for the higher-than-expected blood levels found in the two patients who died.

Health care professionals should continue to follow the Zyprexa Relprevv Patient Care Program REMS requirements and current label recommendations. Notable requirements of the REMS include:

- For a patient to receive treatment, the prescriber, health care facility, patient, and pharmacy must all be enrolled in the Zyprexa Relprevv Patient Care Program.
- Zyprexa Relprevv injections must be administered at a REMS-certified health care facility with ready access to emergency response services.
- Patients must be continuously monitored at the REMS-certified health care facility for at least 3 hours following an intramuscular injection.
- Patients receiving Zyprexa Relprevv must be accompanied to their destination from the health care facility.

Patients should read the [Medication Guide](#) that comes with the Zyprexa Relprevv prescription each time before they get an intramuscular injection, as there may be new information. Patients receiving Zyprexa Relprevv or their caregivers should immediately report symptoms of PDSS to a health care professional. Symptoms of PDSS can include:

- feeling more sleepy than usual
- feeling dizzy
- feeling confused or disoriented
- trouble talking or walking
- feeling weak
- feeling nervous or anxious
- higher blood pressure
- seizures (convulsions)
- passing out (become unconscious or coma).

We urge health care professionals, patients, and caregivers to report side effects involving Zyprexa Relprevv to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.

### **Data Summary**

Following the two unexplained deaths that occurred several days after the patients received intramuscular injections of Zyprexa Relprevv, and as a result of the associated finding of very high postmortem olanzapine blood levels, FDA requested that Eli Lilly and Company conduct an animal study to evaluate whether olanzapine, when injected into muscle, could redistribute after death and thus lead to high levels of the drug in the blood postmortem. If postmortem redistribution were shown to occur, then it could provide an alternative explanation for the high olanzapine levels detected in the blood of the two patients who died; instead of the concern that the patients may have died from post-injection delirium sedation (PDSS) occurring beyond 3 hours after the Zyprexa Relprevv injection.

To test for the postmortem redistribution of olanzapine after injection, investigators measured concentrations of olanzapine and its N-oxide metabolite in antemortem and perimortem samples in animals, and compared the concentrations to those collected postmortem.

Olanzapine concentrations in whole blood obtained postmortem were found to be as much as seven times higher than premortem levels, although the increases were variable in both their

timing and degree of change. In contrast to olanzapine, the concentrations of the N-oxide metabolite tended to decrease after death. The N-oxide metabolite could potentially be converted back to olanzapine during the postmortem phase, and such conversion could have contributed to the rise in olanzapine concentrations postmortem. The study results also suggested that various tissues could act as reservoirs that could contribute to an increase in whole blood olanzapine concentrations after death.

In conclusion, the data show that postmortem redistribution of olanzapine can occur in animals following intramuscular administration of the drug. The postmortem increases in olanzapine concentration in blood appear to be related to redistribution of olanzapine from a variety of tissues.