

### **FDA Drug Safety Communication: FDA warns about rare but serious skin reactions with mental health drug olanzapine (Zyprexa, Zyprexa Zydis, Zyprexa Relprevv, and Symbyax)**

#### **Safety Announcement**

**[05-10-2016]** The U.S. Food and Drug Administration (FDA) is warning that the antipsychotic medicine olanzapine can cause a rare but serious skin reaction that can progress to affect other parts of the body. We are adding a new warning to the drug labels for all olanzapine-containing products that describes this severe condition known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).

**Patients** taking olanzapine-containing products who develop a fever with a rash and swollen lymph glands, or swelling in the face, should seek medical care right away. The combined symptoms together are commonly seen in DRESS. Talk with your health care professional about any questions or concerns. Do not stop taking olanzapine or change your dose without first talking with your health care professional. Sudden stopping of the medicine can be harmful without your health care professional's direct supervision.

**Health care professionals** should immediately stop treatment with olanzapine if DRESS is suspected. When prescribing the medicine, explain the signs and symptoms of severe skin reactions to your patients and tell them when to seek immediate medical care.

Olanzapine is an antipsychotic medicine used to treat mental health disorders schizophrenia and bipolar disorder. It can decrease hallucinations, in which people hear or see things that do not exist, and other psychotic symptoms such as disorganized thinking. Olanzapine is available under the brand names Zyprexa, Zyprexa Zydis, Zyprexa Relprevv, and Symbyax, and also as generics.

DRESS may start as a rash that can spread to all parts of the body. It can include fever and swollen lymph nodes and a swollen face. It causes a higher-than-normal number of infection-fighting white blood cells called eosinophils that can cause inflammation, or swelling. DRESS can result in injury to organs including the liver, kidneys, lungs, heart, or pancreas, and can lead to death.

A search of the [FDA Adverse Event Reporting System \(FAERS\)](#) database identified 23 cases of DRESS reported with olanzapine worldwide since 1996, when the first olanzapine-containing product was approved. FAERS includes only reports submitted to FDA, so there are likely to be additional cases about which we are unaware. One patient taking olanzapine experienced DRESS and died; however, this patient was taking multiple medicines that could also have contributed to death (see Data Summary).

We urge health care professionals, patients, and caregivers to report side effects involving olanzapine (Zyprexa, Zyprexa Zydis, Zyprexa Relprevv, and Symbyax, and generics), or other medicines to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.

### **Facts about Olanzapine**

- Olanzapine is an atypical antipsychotic medicine used to treat schizophrenia and bipolar disorder (manic or mixed episodes). For bipolar disorder, olanzapine can be used alone or in combination with other drugs.
- Olanzapine can decrease hallucinations, in which people hear or see things that do not exist, and other psychotic symptoms such as disorganized thinking. Olanzapine can also decrease the mania of bipolar I disorder.
- Olanzapine is marketed under the brand names Zyprexa, Zyprexa Zydis, Zyprexa Relprevv, and as generic products.
- Olanzapine and fluoxetine are marketed as a combination product under the brand name Symbyax and as generics for the treatment of depressive episodes associated with bipolar I disorder, as well as for depression that has not been successfully relieved by other treatments.
- Common side effects of olanzapine include sleepiness, tiredness, weight gain, increased appetite, low blood pressure, dizziness, muscle stiffness, restlessness, constipation, dry mouth, and tremor or shakiness.
- In 2015, approximately 4.1 million prescriptions for oral olanzapine were dispensed and approximately 849,000 patients received a dispensed prescription for oral olanzapine from U.S. outpatient retail pharmacies.<sup>1</sup>

### **Additional Information for Patients and Caregivers**

- Treatment with olanzapine may cause a rare but severe skin reaction that can spread to cover much of the body. Patients can also develop a fever, rash, swollen lymph nodes, or swelling in the face. The combined symptoms together are known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).
- A new warning to describe DRESS will be added to the labels of all medicines containing olanzapine.
- Call your health care professional(s) and seek immediate medical care if you develop any of the following symptoms:
  - Skin rash
  - Fever
  - Swollen face
  - Swollen lymph glands
- For olanzapine to work properly, the medicine should be taken every day as prescribed.
- Do not stop taking olanzapine or change your dose without first talking to your health care professional. Sudden stopping of the medicine can be harmful without your health care professional’s direct supervision.

- Read the patient [Medication Guide](#) you receive along with your olanzapine prescriptions, which explains the risks associated with the use of olanzapine.
- Discuss any questions or concerns about olanzapine with your health care professional.
- Report any side effects from olanzapine (Zyprexa, Zyprexa Zydis, Zyprexa Relprevv, and Symbyax, and generics), or other medicines to your health care professional and the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of this page

### **Additional Information for Health Care Professionals**

- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), a rare and severe skin reaction accompanied by eosinophilia and systemic signs and symptoms, has been reported in patients treated with drugs that contain olanzapine. Patients may develop fever with rash and lymphadenopathy. Features of DRESS can also include hepatitis, myocarditis, pericarditis, nephritis, pancreatitis, and pneumonitis.
- A new warning to describe DRESS will be added to the labels of all olanzapine-containing drugs.
- When prescribing olanzapine, inform patients about the risk of DRESS, a severe skin reaction that can occur with treatment.
- Explain the signs and symptoms of DRESS to your patients and tell them when to seek immediate medical care if signs and symptoms occur.
- DRESS consists of three or more of the following:
  - Cutaneous reaction (such as rash or exfoliative dermatitis)
  - Eosinophilia
  - Fever
  - Lymphadenopathy
  - One or more systemic complications such as hepatitis, myocarditis, pericarditis, pancreatitis, nephritis, and pneumonitis
- If DRESS is suspected, discontinue olanzapine treatment immediately.
- DRESS is a potentially fatal drug reaction with a mortality rate of up to 10%. The pathogenesis of DRESS is unclear; however, it is thought to be the result of a combination of genetic and immunologic factors, such as detoxification defects in the drug metabolism pathway, resulting in toxic metabolite formation and an immune response. Reactivation of viral infections (herpes virus [HHV-6 or HHV-7]) or Epstein-Barr virus (EBV) may also play a role by inducing or amplifying the immune reaction.
- There is currently no specific treatment for DRESS. The important ways to manage DRESS are early recognition of the syndrome, discontinuation of the offending agent as soon as possible, and supportive care. Treatment with systemic corticosteroids should be considered in cases with extensive organ involvement.
- Report adverse events involving olanzapine (Zyprexa, Zyprexa Zydis, Zyprexa Relprevv, and Symbyax, and generics), or other medicines to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of this page.

## Data Summary

A search of the [FDA Adverse Event Reporting System \(FAERS\)](#) database identified 23 cases of DRESS reported with olanzapine worldwide since 1996, when the first olanzapine-containing product was approved. Of the 23 cases supporting an association between olanzapine and DRESS, one case was fatal. The median time to onset reported in the 23 cases was 19 days after olanzapine treatment was started, and the median duration of olanzapine treatment was 2 months. The median reported olanzapine dose was 20 mg per day, but DRESS was reported at doses as low as 5 mg per day.

With respect to the one fatal case involving DRESS, the autopsy attributed the death to acute cardiac failure related to olanzapine. During the hospitalization, the patient had an initial episode of DRESS, followed by a relapse of DRESS.

The 22 non-fatal cases all reported a serious outcome and 18 of these required hospitalization. One reported the recurrence of DRESS after olanzapine was restarted. Nine cases reported that symptoms completely resolved after discontinuation of olanzapine. Furthermore, there were six cases reporting positive confirmatory test results that were specific for olanzapine reactions. Tests included drug lymphocyte stimulation test, patch test, lymphocyte transformation test, and other allergy workups. Cross-reactivity can occur between olanzapine and other drugs known to cause DRESS because of structural similarities.

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There is currently no specific treatment for DRESS. The keys to managing DRESS are early recognition of the syndrome, discontinuation of the causative agent as soon as possible, and supportive care. Treatment with systemic corticosteroids should be considered in cases with extensive organ involvement.<sup>2</sup>

## References

1. Source: IMS Health, National Prescription Audit (NPA) and Total Patient Tracker (TPT), Extracted April 2016. Prescription and Patient data do not include injectable formulations of olanzapine.
2. Husain Z, Reddy BY, Schwartz RA. DRESS syndrome: Part II. Management and therapeutics. *J Am Acad Dermatol*. 2013 May;68(5):709.e1-9.