

FDA Drug Safety Communication

FDA warns of rare but serious drug reaction to the antiseizure medicines levetiracetam (Keppra, Keppra XR, Elepsia XR, Spritam) and clobazam (Onfi, Sympazan)

Seek immediate medical attention if unexplained rash, fever, or swollen lymph nodes develop

11-28-2023 FDA Drug Safety Communication

What safety concern is FDA announcing?

The U.S. Food and Drug Administration (FDA) is warning that the antiseizure medicines levetiracetam (Keppra, Keppra XR, Elepsia XR, Spritam) and clobazam (Onfi, Sympazan), can cause a rare but serious reaction that can be life-threatening if not diagnosed and treated quickly. This reaction is called Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). It may start as a rash but can quickly progress, resulting in injury to internal organs, the need for hospitalization, and even death. As a result, we are requiring warnings about this risk to be added to the [prescribing information](#) and patient [Medication Guides](#) for these medicines.

This hypersensitivity reaction to these medicines is serious but rare. DRESS can include fever, rash, swollen lymph nodes, or injury to organs including the liver, kidneys, lungs, heart, or pancreas.

What is FDA doing?

We are requiring manufacturers of these medicines to add new warnings about DRESS to the [prescribing information](#) and the [Medication Guide](#) for patients and caregivers. For levetiracetam (Keppra, Keppra XR, Elepsia XR, and Spritam), this involves adding a new warning in the *Warnings and Precautions* section of the [prescribing information](#), which describes the most serious and significant potential safety issues.¹ Currently the symptoms associated with this condition are described less prominently. For clobazam (Onfi and Sympazan), we are requiring a new warning specifically about DRESS to be added to the [prescribing information](#). Symptoms related to this risk are already described more generally in other sections of the clobazam [prescribing information](#).

The warnings for both levetiracetam and clobazam medicines will include information that early symptoms of DRESS such as fever or swollen lymph nodes can be present even when a rash cannot be seen. This is different from other serious skin-related reactions that can happen with these medicines and where a rash is present early on, including Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN). We are also requiring information on this risk to be added to the [Medication Guides](#) to help inform patients and caregivers about this risk.

What are levetiracetam (Keppra, Keppra XR, Elepsia XR, Spritam) and clobazam (Onfi, Sympazan), and how can these medicines help me?

Levetiracetam is an antiseizure medicine approved for use alone or with other medicines to control certain types of seizures. It has been FDA-approved for 24 years and is available in multiple formulations under the brand names Keppra, Keppra XR, Elepsia XR, and Spritam, and as generics.

Clobazam is a type of medicine called a benzodiazepine that is FDA-approved for use with other

¹ <https://www.fda.gov/about-fda/oncology-center-excellence/how-do-i-use-prescription-drug-labeling#Section-5>

medicines to control seizures associated with a specific severe form of epilepsy called Lennox-Gastaut Syndrome. Benzodiazepines are a class of medicines that depress the central nervous system. DRESS and other serious skin reactions reported with clobazam have generally been associated only with clobazam and not with other benzodiazepines. Clobazam has been FDA-approved for 12 years. It is available in multiple formulations under the brand names Onfi and Sympazan, and as generics.

What should patients and caregivers do?

Do not stop taking levetiracetam or clobazam without talking with your health care professional. Stopping these medicines suddenly can lead to uncontrolled seizures. It is important to seek immediate medical attention for DRESS. Patients who develop any unusual symptoms or reactions, including a rash, at any time while taking levetiracetam or clobazam should go to an emergency room immediately. Fever with a rash and swollen lymph nodes or swelling in the face are common with DRESS, but some patients may not develop a rash. Symptoms of DRESS generally start 2 weeks to 8 weeks after starting on the medicine, but these symptoms may occur earlier or later. A physical examination, laboratory blood tests, and other evaluations are used to diagnose DRESS.

What should health care professionals do?

Health care professionals should be aware that prompt recognition and early treatment is important for improving DRESS outcomes and decreasing mortality. Diagnosis is often difficult because early signs and symptoms such as fever and swollen lymph nodes may be present without evidence of a rash. DRESS can develop 2 weeks to 8 weeks after starting the medicines, and symptoms and intensity can vary widely. DRESS can also be confused with other serious skin reactions such as SJS and TEN. Advise patients of the signs and symptoms of DRESS and to stop taking their medicine and seek immediate medical attention if DRESS is suspected during treatment with levetiracetam or clobazam.

What did FDA find?

FDA's cumulative review found serious cases of DRESS in children and adults worldwide (32 for levetiracetam and 10 for clobazam, see Data Summary). Most patients in these cases required hospitalization and received medical treatments, and two patients treated with levetiracetam died. These numbers include only reports submitted to FDA* and found in the medical literature, so there are likely additional cases about which we are unaware. We determined there was reasonable evidence that levetiracetam** and clobazam‡ were the cause of DRESS in these cases based on the timing of the onset of these events after receiving the medicines and the order in which they occurred. The majority of cases for which information about discontinuation was available reported that DRESS symptoms improved when the medicines were discontinued.

*The cases were reported to the [FDA Adverse Event Reporting System \(FAERS\) database](#).

**We previously communicated safety information associated with levetiracetam in [December 2008](#) (suicidal behavior and ideation and antiepileptic drugs).

‡We previously communicated safety information associated with clobazam in [August 2016](#) (serious risks and death when combining opioid pain or cough medicines with benzodiazepines), [September 2017](#) (caution about withholding opioid addiction medicines from patients taking benzodiazepines or CNS depressants), and [December 2013](#) (rare but serious skin reactions called SJS and TEN).

What is my risk?

All medicines have side effects even when used correctly as prescribed. It is important to know that people respond differently to all medicines depending on their health, the diseases they have, genetic factors, other medicines they are taking, and many other factors. As a result, we cannot determine how likely it is that someone will experience DRESS, a rare but serious reaction, when taking levetiracetam or

clobazam. Your health care professional knows you best, so talk to them if you have questions or concerns about the risks of taking these medicines.

How do I report side effects from levetiracetam or clobazam?

To help FDA track safety issues with medicines, we urge patients and health care professionals to report side effects involving levetiracetam or clobazam, or other medicines, to the FDA MedWatch program using the information in the “Contact FDA” box at the bottom of this page.

How can I get new safety information on medicines I’m prescribing or taking?

You can sign up for [email alerts](#) about Drug Safety Communications on medicines or medical specialties of interest to you.

Facts about Levetiracetam (Keppra, Keppra XR, Elepsia XR, Spritam)

- Levetiracetam is an antiseizure medicine indicated for use alone or together with other medicines to control certain types of seizures in adults and children such as partial seizures, myoclonic seizures, or tonic-clonic seizures.
- Levetiracetam is available as a liquid solution, immediate- and extended-release tablets, and a tablet that must be dissolved in a small amount of water on the tongue.
- Common side effects of levetiracetam include unusual irritability or aggression, confusion, loss of balance or coordination, and extreme drowsiness.
- In 2022, an estimated 12 million levetiracetam prescriptions were dispensed from U.S. outpatient pharmacies.¹

Facts about Clobazam (Onfi, Sympazan)

- Clobazam is a benzodiazepine indicated for use in combination with other medicines to control seizures in adults and children 2 years and older who have a specific severe form of epilepsy called Lennox-Gastaut syndrome.
- Clobazam is available as a tablet and a liquid suspension (a powder mixed in a liquid) taken by mouth, and as a film applied on the tongue to dissolve.
- Common side effects of clobazam include difficulty speaking or swallowing, tiredness, change in appetite, and problems with muscle control or coordination.
- In 2022, an estimated 779,000 clobazam prescriptions were dispensed from U.S. outpatient pharmacies.¹

Additional Information for Patients and Caregivers

- The medicines levetiracetam (Keppra, Keppra XR, Elepsia XR, Spritam) and clobazam (Onfi, Sympazan) prescribed to reduce seizures have been associated with a rare but serious reaction called Drug Reaction with Eosinophilia and Systemic Symptoms, or DRESS.
- This serious sensitivity is a reaction of the immune system that can cause severe swelling (inflammation) throughout the body, or injury to organs, including the liver, kidneys, lungs, heart, or pancreas. It can lead to hospitalization and damage or failure of these organs and may progress to death, especially if treatment is delayed.
- Do not stop taking your levetiracetam or clobazam medicines without first talking to your health care professional. Stopping suddenly can cause uncontrolled seizures.
- Signs and symptoms of DRESS have been reported to occur 2 weeks to 8 weeks after starting to take levetiracetam or clobazam, but may occur earlier or later.

- Call your health care professional and seek immediate medical attention if you develop any of the following symptoms at any time while taking levetiracetam or clobazam:
 - Fever
 - Swollen lymph nodes
 - Sore throat
 - Skin rash (may or may not be present)
 - Swelling of your face, or eyes
 - Painful sores in the mouth or around your eyes
 - Trouble swallowing or breathing
 - Yellowing of your skin or eyes
 - Unusual bruising or bleeding
 - Severe fatigue or weakness
 - Shortness of breath or exercise intolerance
 - Severe muscle pain
- Read the patient [Medication Guide](#) every time you receive a prescription for your medicines because there may be new or important additional information about them. The [Medication Guide](#) explains the important things you need to know about the medicine. These include the side effects, what the medicine is used for, how to take and store it properly, and things to watch for when you are taking the medicine.
- To help FDA track safety issues with medicines, report side effects from levetiracetam or clobazam, or other medicines, to the FDA MedWatch program using the information in the “Contact FDA” box at the bottom of this page.
- You can sign up for [email alerts](#) about Drug Safety Communications on medicines and medical specialties of interest to you.

Additional Information for Health Care Professionals

- Levetiracetam (Keppra, Keppra XR, Elepsia XR, Spritam) and clobazam (Onfi, Sympazan) have been associated with a rare but serious and potentially life-threatening sensitivity reaction called Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) that typically occurs 2 weeks to 8 weeks after starting these medicines.
- This reaction can cause severe inflammation and organ injury throughout the body that may require hospitalization or lead to death, particularly if diagnosis and treatment are delayed. Eosinophilia is often but not always present.
- We are requiring the risk of DRESS to be added to the *Warnings and Precautions* sections of the [prescribing information and](#) to the [Medication Guides](#). The risk of DRESS is currently in the Adverse Reactions; Postmarketing Experience section of the levetiracetam [prescribing information](#), and symptoms related to this risk are already described more generally in other sections of the clobazam [prescribing information](#).
- When prescribing levetiracetam or clobazam, inform patients about the risk of DRESS.
- Explain the signs and symptoms of DRESS and tell patients when to seek immediate medical care if any of these occur.
- DRESS consists of a combination of the following:
 - Cutaneous reaction (such as generalized rash or exfoliative dermatitis, which may or may not be present)
 - Eosinophilia
 - Fever

- Lymphadenopathy
- One or more systemic complications such as hepatitis, myocarditis, pericarditis, pancreatitis, nephritis, and pneumonitis
- If DRESS is suspected, discontinue levetiracetam or clobazam immediately and restart only if an alternative etiology for the signs or symptoms cannot be established.
- Important ways to manage DRESS are early recognition, discontinuation of the offending agent as soon as possible, supportive care, and/or other interventions commonly used to treat DRESS such as systemic corticosteroids.
- Encourage patients to read the [Medication Guide](#) they receive with their prescriptions because there may be new or important additional information about the medicine.
- To help FDA track safety issues with medicines, report adverse events involving levetiracetam or clobazam, or other medicines, to the FDA MedWatch program using the information in the “Contact FDA” box at the bottom of this page.
- You can sign up for [email alerts](#) about Drug Safety Communications on medicines and medical specialties of interest to you.

Data Summary

FDA reviewed worldwide cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) associated with levetiracetam and clobazam in children and adults reported to the [FDA Adverse Event Reporting System \(FAERS\) database](#) and found in the medical literature.

Levetiracetam

A search of FAERS and the medical literature through March 2023 identified 32 serious cases of DRESS worldwide. Three cases occurred in the U.S. and 29 abroad. In all 32 cases, the patients were hospitalized and received medical treatment; in two cases the patients died. The median time to onset was 24 days (range 7 to 170 days). The reported signs and symptoms included skin rash (n=22), fever (n=20), eosinophilia (n=17), lymph node swelling (n=9), and atypical lymphocytes (n=4). Twenty-two cases reported injury to one or more organs, including the liver (n=20), lungs (n=4), kidneys (n=3), and gallbladder (n=1). Twenty-five of the 29 cases for which information on treatment discontinuation was available reported that DRESS symptoms resolved when levetiracetam was discontinued.

Clobazam

A search of FAERS and the medical literature through July 2023 identified 10 serious cases of DRESS worldwide, one in the U.S. and nine abroad. In all 10, the patients were hospitalized and received medical treatment. No deaths were reported. The median time to onset was 21.5 days (range 7 to 103 days). The reported signs and symptoms included skin rash (n=10), fever (n=8), eosinophilia (n=7), facial swelling (n=7), leukocytosis (n=4), lymph node swelling (n=4), and leukopenia/thrombocytopenia (n=1). Nine cases reported injury to one or more organs, including the liver (n=7), kidneys (n=3), and gastrointestinal tract (n=1). DRESS symptoms resolved in all 10 when clobazam was discontinued. DRESS and other serious skin reactions reported with clobazam have not generally been associated with other benzodiazepines.

Reference

1. IQVIA. U.S. National Data, National Prescription Audit (NPA) database. Data Extracted November 2023. <https://www.iqvia.com/insights/the-iqvia-institute/available-iqvia-data>

Related Information

- [Drug Reaction with Eosinophilia and Systemic Symptoms \(DRESS\)](#)
- [Seizures](#)
- [The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective](#)
- [Think It Through: Managing the Benefits and Risks of Medicines](#)