

**Office of Integrated Health
Health & Safety Information**

Dr. Dawn M. Adams DNP, ANP-BC, CHC
Director, Office of Integrated Health

Drug Safety Communication - Serious Immune System Reaction

The following information is provided by the U.S. Department of Health and Human Services Food & Drug Administration

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AUDIENCE: Health Professional, Patient, Pharmacy

ISSUE: The FDA is warning that the medicine **Lamictal (lamotrigine)** for seizures and bipolar disorder can cause a rare but very serious reaction that excessively activates the body's infection-fighting immune system. This can cause severe inflammation throughout the body and lead to hospitalization and death, especially if the reaction is not diagnosed and treated quickly. As a result, we are requiring a new warning about this risk be added to the prescribing information in the lamotrigine drug labels.

BACKGROUND: The immune system reaction, called hemophagocytic lymphohistiocytosis (HLH), causes an uncontrolled response by the immune system. HLH typically presents as a persistent fever, usually greater than 101°F, and it can lead to severe problems with blood cells and organs throughout the body such as the liver, kidneys, and lungs.

Lamotrigine is used alone or with other medicines to treat seizures in patients two years and older. It may also be used as maintenance treatment in patients with bipolar disorder to help delay the occurrence of mood episodes such as depression, mania, or hypomania. Stopping lamotrigine without first talking to a prescriber can lead to uncontrolled seizures, or new or worsening mental health problems. Lamotrigine has been approved and on the market for 24 years, and is available under the brand name Lamictal and as generics.

RECOMMENDATION: Healthcare professionals should be aware that prompt recognition and early treatment is important for improving HLH outcomes and decreasing mortality. Diagnosis is often complicated because early signs and symptoms such as fever and rash are not specific. HLH may also be confused with other serious immune-related adverse reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).

Evaluate patients who develop fever or rash promptly, and discontinue lamotrigine if HLH or another serious immune-related adverse reaction is suspected and an alternative etiology for the signs and symptoms cannot be established. Advise patients to seek immediate medical attention if they experience symptoms of HLH during lamotrigine treatment. A diagnosis of HLH can be established if a patient has at least five of the following eight signs or symptoms:

- fever and rash
- enlarged spleen
- cytopenias
- elevated levels of triglycerides or low blood levels of fibrinogen
- high levels of blood ferritin
- hemophagocytosis identified through bone marrow, spleen, or lymph node biopsy
- decreased or absent Natural Killer (NK) Cell activity
- elevated blood levels of CD25 showing prolonged immune cell activation

Patients or their caregivers should contact their health care professionals right away if they experience any symptom of HLH while taking lamotrigine. HLH can occur within days to weeks after starting treatment. A physical examination and specific laboratory blood tests and other evaluations are used to diagnose HLH. Signs and symptoms of HLH include but are not limited to:

- fever
- enlarged liver; symptoms may include pain, tenderness, or unusual swelling over the liver area in the upper right belly
- swollen lymph nodes
- skin rashes
- yellow skin or eyes
- unusual bleeding
- nervous system problems, including seizures, trouble walking, difficulty seeing, or other visual disturbances

Read the patient Medication Guide, which explains the benefits and risks of lamotrigine, every time you get a new prescription because the information may change. Do not stop taking lamotrigine without talking to your health care professional first as doing so can cause serious problems.

Healthcare professionals and patients are encouraged to report adverse events or side effects related to the use of these products to the FDA's MedWatch Safety Information and Adverse Event Reporting Program:

- Complete and submit the report Online: www.fda.gov/MedWatch/report
- Download form or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form, or submit by fax to 1-800-FDA-0178

Source:

<https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm605628.htm>
