



### FDA warns of serious immune system reaction with seizure and mental health medicine lamotrigine (Lamictal)

#### Safety Announcement

**[04-25-2018]** The Food and Drug Administration (FDA) is warning that the medicine lamotrigine (Lamictal) 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](#).\*

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.

**Health care 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.

In the 24 years since lamotrigine's 1994 approval, FDA identified eight cases worldwide of confirmed or suspected HLH associated with the medicine in children and adults (see Data Summary). This number includes only reports submitted to FDA<sup>±</sup> and found in the medical literature, so there are likely additional cases about which we are unaware. We determined there was reasonable evidence that lamotrigine was the cause of HLH in these eight cases based on the timing of events and the order in which they occurred. The patients in these cases required hospitalization and received drug and other medical treatments, with one dying.

We previously communicated safety information associated with lamotrigine in [September 2006](#) (possible association between Lamictal exposure during pregnancy and oral clefts in newborns) and [August 2010](#) (aseptic meningitis warning). Lamotrigine was also covered as part of a [May 2009](#) safety alert concerning suicidal thoughts and behavior with the entire class of anti-seizure medicines.

We urge health care professionals and patients to report side effects involving lamotrigine (Lamictal) and other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

\*For additional drug label information, search [Drugs@FDA: FDA Approved Drug Products](#).

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

## **Facts about Lamotrigine (Lamictal)**

- Lamotrigine is used alone or with other medicines to treat seizures in patients two years and older. Use of lamotrigine as a single drug to treat seizures is approved only in patients 16 and older.
- Lamotrigine is also used as maintenance treatment in adults with bipolar disorder to help delay the occurrence of mood episodes such as depression, mania, or hypomania.
- In addition to HLH, lamotrigine can cause a number of other serious adverse reactions already included in the drug label such as:
  - Rashes, including serious rashes that may need to be treated in a hospital and may cause permanent disability or death
  - Serious allergic reactions that may cause problems affecting the blood, liver, and other organs
  - Suicidal thoughts and actions
  - Aseptic meningitis, a serious inflammation or swelling, of the protective membrane that covers the brain and spinal cord
- Less serious side effects may include dizziness, sleepiness, headache, double vision, blurred vision, nausea, vomiting, and loss of coordination.
- Lamotrigine is available as a tablet to be swallowed, a tablet that dissolves on the tongue (Lamictal ODT), a chewable tablet (Lamictal CD), and as an extended-release tablet (Lamictal XR).

### **Additional Information for Patients**

- The medicine lamotrigine (Lamictal), prescribed for seizures and bipolar disorder, has been associated with a rare but very serious reaction in which the body's immune system is excessively activated, called hemophagocytic lymphohistiocytosis (HLH). This can cause severe inflammation, or swelling, throughout the body and lead to hospitalization or death, especially if treatment is delayed.
- This uncontrolled, excessive immune response can lead to damage or failure of many organs and may progress to death.
- HLH can be caused by an underlying genetic disorder or a gene mutation, or it may be triggered by different conditions, including infections, cancer, and autoimmune diseases. In a small number of cases it can be caused by drugs, including lamotrigine.
- FDA is requiring a new warning about the risk of HLH to be added to the prescribing information in the lamotrigine [drug labels](#).
- Do not stop taking your lamotrigine medicine without first talking to your health care professional. Stopping it suddenly can potentially cause uncontrolled seizures, or new or worsening mental health problems.
- Symptoms of HLH have been reported to occur within 8 to 24 days after the first dose is taken. Contact your doctor right away if you have symptoms of HLH at any time while taking lamotrigine.
- Seek medical attention immediately if you experience any symptoms of HLH while taking lamotrigine. Symptoms of HLH include:
  - Fever, usually  $>101^{\circ}\text{F}$
  - 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
- Talk to your health care professional if you have questions or concerns about lamotrigine.
- Report side effects from lamotrigine (Lamictal) or other medicines to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of this page.

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

- Lamotrigine (Lamictal) has been associated with a rare, but serious and life-threatening adverse reaction called hemophagocytic lymphohistiocytosis (HLH), which can lead to multi-organ failure resulting in hospitalization or death, particularly if diagnosis and treatment are delayed.
- Conduct a medical evaluation as soon as suspicious symptoms are reported and discontinue lamotrigine if HLH is suspected, confirming diagnosis with laboratory tests and other studies. Patients with suspected HLH should be evaluated by a hematologist.
- Diagnosis is often complicated because early signs and symptoms are non-specific, including fever and rash, and HLH can be confused with other serious immune-related adverse reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).
- FDA is requiring a new warning about the risk of HLH to be added to the prescribing information in the lamotrigine [drug labels](#).
- In the eight cases FDA studied, symptoms of HLH were reported to have occurred within 8 to 24 days following treatment initiation.
- Tell patients about the symptoms of HLH and advise them to seek medical attention immediately if they experience these symptoms during lamotrigine treatment.
- A diagnosis of HLH can be established if a patient has at least five of the following eight signs or symptoms, according to the published international diagnostic criteria for HLH, known as [HLH-2004 diagnostic criteria](#). These include:
  1. Fever
  2. Splenomegaly
  3. Cytopenias affecting  $\geq 2$  of 3 lineages in the peripheral blood:
    - a. Hemoglobin  $< 90$  g/L (in infants  $< 4$  weeks: hemoglobin  $< 100$  g/L)
    - b. Platelets  $< 100 \times 10^9/L$
    - c. Neutrophils  $< 1.0 \times 10^9/L$
  4. Hypertriglyceridemia and/or hypofibrinogenemia:
    - a. Fasting triglycerides  $\geq 3.0$  mmol/L (i.e.,  $\geq 265$  mg/dl)
    - b. Fibrinogen  $\leq 1.5$  g/L
  5. Hemophagocytosis in bone marrow or spleen or lymph nodes
  6. Low or absent Natural Killer (NK) cell activity
  7. Ferritin  $\geq 500$   $\mu\text{g/L}$
  8. Soluble CD25 (i.e., soluble IL-2 receptor)  $\geq 2,400$  U/ml
- Lamotrigine may cause other serious adverse reactions such as:

- Serious skin rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis
- Multi-organ hypersensitivity reactions and organ failure
- [Suicidal thoughts or actions](#)
- [Aseptic meningitis](#)
- Tell patients that sudden stopping of lamotrigine treatment can potentially cause uncontrolled seizures, or new or worsening mental health problems. Advise them to seek medical attention immediately if they develop any suggestive symptoms to discuss whether stopping Lamotrigine is appropriate.
- Encourage patients to read the patient [Medication Guide](#) they receive with their lamotrigine prescriptions, which explains its benefits and risks.
- Report adverse events involving lamotrigine (Lamictal) or other medicines to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of this page.

## Data Summary

We identified eight worldwide cases of confirmed or suspected hemophagocytic lymphohistiocytosis (HLH) associated with lamotrigine use in children and adults reported in the FDA Adverse Event Reporting System (FAERS) database and/or the medical literature from December 1994 through September 2017. Two cases occurred in the U.S. and six occurred abroad.

Five cases had confirmed HLH, fulfilling five of the eight [HLH-2004 diagnostic criteria](#). Three cases had suspected HLH, fulfilling four of the eight HLH-2004 diagnostic criteria. The eight cases had signs and symptoms including fever (n=8), thrombocytopenia (n=8), hyperferritinemia (n=8), hypofibrinogenemia (n=5), splenomegaly (n=3), anemia (n=3), hypertriglyceridemia (n=2), low or absent Natural Killer (NK) cells (n=1), and neutropenia (n=1). All eight cases had positive bone marrow biopsies consistent with hemophagocytosis.

All cases were reported to have serious outcomes. All eight reported hospitalization, three reported other serious important medical events, two reported the outcome as being life-threatening, and one reported death. All cases had a plausible temporal relationship with lamotrigine, occurring within 24 days of starting lamotrigine treatment. Doses ranged from 25 mg every other day to 250 mg once daily in the six cases that reported this information. In seven cases, HLH improved after treatment and discontinuation of Lamictal, and one case did not improve and had a fatal outcome. No cases reported rechallenge. Treatment reported in the eight cases included steroids (n=6), intravenous immunoglobulin (n=4), blood products (n=2), and chemotherapy (n=2).

All eight cases reported concomitant medications. None of the concomitant medications are associated with HLH.

## References

1. Fukaya S, Yasuda S, Hashimoto T, et al. Clinical features of haemophagocytic syndrome in patients with systemic autoimmune diseases: analysis of 30 cases. *Rheumatology*. 2008 Nov;47(11):1686-91.
2. Henter J, Horne A, Aricó M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2007;48:124–131.
3. Jordan MB, Allen CE, Weitzman S et al. How I treat hemophagocytic lymphohistiocytosis. *Blood* 2011;118:4041-4052.
4. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, et al. Adult haemophagocytic syndrome. *Lancet* 2014; 383: 1503–1516.

### **Related Information**

- [Hemophagocytic Lymphohistiocytosis](#)
- [Seizures](#)
- [The Facts on Bipolar Disorder and FDA-Approved Treatments](#)
- [The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective](#)
- [Think It Through: Managing the Benefits and Risks of Medicines](#)