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Introduction

The International League Against Epilepsy (ILAE)/American Epilepsy Society (AES) Task Force on the cardiac effects of lamotrigine was convened in response to a recent addition to the lamotrigine label by the US Food and Drug Administration (FDA).¹ Lamotrigine is the nonproprietary name for a medicine that is sold under its generic name and several brand names including Lamictal™. The present advisory is based on an assessment of currently available evidence. It is not intended to replace regulatory requirements nor is it intended to be an exhaustive review. Its purpose is to advise health care professionals worldwide on how to minimize cardiac safety risks associated with lamotrigine use.

What Was Added to the United States Label?

The following 2 paragraphs were added:¹

Warnings and precautions (5.4) Cardiac Rhythm and Conduction Abnormalities: In vitro testing showed that Lamictal exhibits Class IB antiarrhythmic activity at therapeutically relevant concentrations [see *Clinical Pharmacology (12.2)*]. Based on this activity, Lamictal (lamotrigine) could slow ventricular conduction (widen QRS) and induce proarrhythmia, including sudden death, in people with structural heart disease or myocardial ischemia. Therefore, avoid the use of Lamictal in people who have cardiac conduction disorders (eg, second- or third-degree heart block), ventricular arrhythmias, or cardiac disease or abnormality (eg, myocardial ischemia, heart failure, structural heart disease, Brugada syndrome, or other sodium channelopathies). Concomitant use of other sodium channel blockers may increase the risk of proarrhythmia.

Clinical Pharmacology (12.2). Effect of Lamictal: In vitro studies show that lamotrigine exhibits Class IB antiarrhythmic activity at therapeutically relevant concentrations. It inhibits human cardiac sodium channels with rapid onset and offset



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kinetics and strong voltage dependence, consistent with other Class IB antiarrhythmic agents. Lamictal did not slow ventricular conduction (widen QRS) in healthy individuals in a thorough QT study; however, it could slow ventricular conduction and increase the risk of arrhythmia in people with structural heart disease or myocardial ischemia. Elevated heart rates could also increase the risk of ventricular conduction slowing with Lamictal.

Have Regulatory Agencies Other Than the FDA Added Any Warning?

To date, the European Medicines Agency has not added any warnings, and we know of no new warnings from other countries at this time.

Are These Warnings and Precautions Only Relevant to Lamotrigine or Are They Also Applicable for Other Sodium Channel Blockers?

The cardiac concerns stem from lamotrigine's sodium channel blocking properties. No differences in the occurrence of electrocardiogram (EKG) abnormalities have been reported in 2 small studies that compared lamotrigine with carbamazepine,^{2,3} including specifically elderly individuals with epilepsy.² However, we are not aware of any head-to-head comparative thorough clinical study of the effects of lamotrigine and other sodium channel blockers on cardiac electrophysiology. A synergistic pharmacodynamic interaction with other substances with sodium channel blocking properties may be expected, and potentially increase the risk for adverse cardiac effects (see also item #10).

These Warnings Stem From *In Vitro* Data. Are These Data Available?

We are aware of a previous study by Harmer et al⁴ that raised concerns at the FDA. While that study has limitations that bring its clinical relevance into question, it is our understanding that it led to a request by the FDA for a subsequent *in vitro* study from Lamictal's manufacturer, Glaxo Smith-Kline (GSK). As per GSK, that work was completed in 2019 and showed that lamotrigine can weakly inhibit cardiac sodium channels, showing Class IB antiarrhythmic activity. That *in vitro* information led to the recent US package insert update and warning. The task force has requested the *in vitro* data from GSK, but to date this has not been provided.

Have Human Studies Been Performed to Evaluate This?

While *in vitro* data indicate lamotrigine has Class IB antiarrhythmic sodium channel blocking properties, there is no change in ventricular conduction (QRS duration) in healthy individuals⁵ and individuals with epilepsy without heart

disease.² A modest increase in the atrioventricular conduction interval (PR prolongation) may occur, especially at high doses.⁶ Significantly, unlike Class IA anti-arrhythmic drugs, lamotrigine does not prolong repolarization (no change in QT) in healthy people at thorough QT testing.⁵ At high doses of lamotrigine, there is a mild QT shortening observed,⁵ which is a Class IB property. Thus, based on the absence of QRS or QT changes, and only mild PR prolongation even at high doses, there is not an apparent arrhythmia risk of lamotrigine therapy in healthy people without heart disease.^{5,6} It should also be noted that the Class IB antiarrhythmic drugs lidocaine and mexiletine have a long record of use in people with ischemic heart disease.

Are There Any Data That Arrhythmias or Sudden Deaths Due to Cardiac Issues Are More Common in People on Lamotrigine Compared to Other Anti-Seizure Medications?

To our knowledge, an increased risk of arrhythmias or sudden deaths due to cardiac issues or need for pacemaker therapy in people on lamotrigine as compared to other anti-seizure medications (ASMs) has not been demonstrated. Sudden Unexpected Death in Epilepsy (SUDEP) is, however, relatively common in people with epilepsy. In adults with epilepsy, the overall rate of SUDEP is approximately 1:1000/year, but the risk is higher in people with frequent convulsive seizures.⁷ Thus, an increase in sudden cardiac death caused by lamotrigine could theoretically be missed if it occurred at a very low frequency in relation to SUDEP risk.

The Warning States That Lamotrigine Could Pose a Risk to People With Underlying Cardiac Disease and Not Healthy Individuals. Should I be Performing EKGs in My Healthy Patients to Look for Underlying Cardiac Disease?

The risk of undiagnosed asymptomatic cardiac disease under the age of 60 years is minimal in the absence of major cardiovascular risk factors such as diabetes, hypertension, familial hypercholesterolemia, and smoking. In people over the age of 60 years, the likelihood of undiagnosed cardiac conduction abnormalities increases, and an EKG may be considered prior to initiating lamotrigine. An EKG should also be considered in people younger than 60 with known cardiac disease or significant risk factors as above.

If I Perform an EKG and It Is Abnormal, Does That Mean I Should Not Initiate Lamotrigine?

Nonspecific EKG abnormalities (eg, nonspecific ST and T wave abnormalities) are not concerning, and should not preclude these individuals from being prescribed lamotrigine.



The highest risk cases are those with second-, third-degree heart block, Brugada syndrome, arrhythmogenic ventricular cardiomyopathy, left bundle branch block, and right bundle branch block with left anterior or posterior fascicular block. These patients require thorough cardiological investigation to determine whether lamotrigine can be administered safely. If there are concerns, consultation with a cardiologist before initiating lamotrigine may be warranted.

Often ASMs Need to be Initiated as Quickly as Possible After a Diagnosis of Epilepsy Is Made. Do I Have to Wait to Start Lamotrigine Until I Obtain the Results of the EKG?

In most cases the initial EKG can be obtained while titrating, mainly when the individual is at the first dose of 25 mg/d because lamotrigine must be titrated slowly, and because cardiac adverse events are dose-related.

Once an Individual Is on Lamotrigine, Does the EKG Need to be Repeated?

If used in people at risk, a repeat EKG should be considered at the target dose, mainly when the target dose (or the serum lamotrigine level) is near or above the upper limit of the therapeutic range, and always in the presence of concomitant use of other sodium channel blockers or substances known to impair atrio-ventricular and/or intra-ventricular cardiac conduction. Because concomitant use of such drugs put people at increased risk for impaired cardiac conduction when adding lamotrigine, an initial EKG should also be performed.

Are There Any Other Cardiovascular Situations That I Should Worry About, Particularly for People Who Are Already on Lamotrigine?

Clinicians should consider obtaining an EKG and/or cardiology consultation in people on lamotrigine with sudden-onset syncope or presyncope with loss of muscular tone without a clear vasovagal or orthostatic cause.

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