



FDA Safety Warning on the Cardiac Effects of Lamotrigine: An Advisory from the Ad Hoc ILAE/AES Task Force

Co-chairs: Jacqueline A. French¹, Emilio Perucca²

ILAE members: Josemir W. Sander^{3,4}, Lennart Bergfeldt⁵, Michel Baulac⁶

Advisory: David S. Auerbach⁷, Mark Keezer^{4,8}, Roland D. Thijs^{3,4,9}, Orrin Devinsky¹

American Epilepsy Society (AES) contributors: David G. Vossler¹⁰, Timothy E. Welty¹¹

25 Feb 2021

¹ Department of Neurology, New York University Grossman School of Medicine and NYU Langone Health, New York, NY, USA

² Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy

³ UCL Queen Square Institute of Neurology, London WC1N 3BG, and Chalfont Centre for Epilepsy, Chalfont St Peter SL9 0RJ, United Kingdom,

⁴ Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede 2103 SW, The Netherlands

⁵ Department of Molecular & Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, and Department of Cardiology, Sahlgrenska University Hospital, Gothenburg, Sweden

⁶ Sorbonne Université, ICM, Department of Neurology, Salpêtrière University Hospital, AP-HP, Paris, France.

⁷ Department of Pharmacology, SUNY Upstate Medical University, Syracuse, NY, USA

⁸ Department of Neurosciences & School of Public Health of the Université de Montréal, Montreal, Canada

⁹ Department of Neurology, Leiden University Medical Centre, Leiden, The Netherlands

¹⁰ University of Washington, Seattle, WA, USA

¹¹ College of Pharmacy and Health Sciences, Drake University, Des Moines, IA, USA

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 non-proprietary 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 healthcare professionals worldwide on how to minimize cardiac safety risks associated with lamotrigine use.

WHAT WAS ADDED TO THE U.S. LABEL?

The following two paragraphs were added¹:

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 (e.g., second- or third-degree heart block), ventricular arrhythmias, or cardiac disease or abnormality (e.g., 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 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 (EMA) 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 EKG abnormalities have been reported in two 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 al.⁴ 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 1B 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 AV conduction interval (PR prolongation) may occur, especially at high doses.⁶ Significantly, unlike Class 1A 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 observed⁵, 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 ANTISEIZURE MEDICATIONS (ASMs)?

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 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?

Non-specific EKG abnormalities (e.g., non-specific 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 2nd, 3rd-degree heart block, Brugada syndrome, arrhythmogenic ventricular cardiomyopathy (ARVC), left bundle branch block (LBBB), and right bundle branch block (RBBB) with left anterior or posterior fascicular block. These patients require thorough cardiological investigation to determine if 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/day 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 pre-syncope with loss of muscular tone without a clear vasovagal or orthostatic cause.

ACKNOWLEDGEMENTS

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. This document was written with the contribution of experts selected by the International League Against Epilepsy (ILAE) and was approved for publication by the ILAE. Opinions expressed by the authors, however, do not necessarily represent the policy or position of the ILAE. Appreciation is expressed to Aatif Husain, MD, Chair of the AES Guidelines and Assessment Committee, for the early alert of the potential significance of the FDA warning to providers and patients and to Barry Gidal, PharmD, Chair of the American Epilepsy Society (AES) Treatments Committee, for facilitating AES-ILAE collaboration on this advisory statement.

CONFLICT OF INTEREST

DGV's institution receives payment for his work as principal investigator on antiseizure medication trials for SK Life Science and Xenon, Inc. EP received speaker's or consultancy fees from Amicus Therapeutics, Arvelle, Biogen, Corlieve, Eisai, GW Pharma, Intas Pharmaceuticals, Laboratorios Bagò, Sanofi, Sun Pharma, UCB Pharma and Xenon Pharma. JWS reports personal fees from Eisai, UCB, Arvelle and Zogenix. MB received speaker's or consultancy fees from Arvelle therapeutics, Eisai, GSK, GW Pharma, UCB Pharma, and Zogenix. MK receives salary support from the Fonds de Recherche Québec – Santé (chercheur-clinicien junior 1), reports unrestricted educational grants from UCB and Eisai, and research grants for investigator-initiated studies from UCB and Eisai, as well as research grants from the Canadian Frailty Network, the Savoy Foundation, and the Canadian Institutes of Health Research. OD has equity interests in Qstate Biosciences, Tevard Biosciences, Regel

Therapeutics and Script Biosciences, Tilray, Receptor Life Sciences, Empatica, Engage, Papa & Barkley, Rettco, SilverSpike, and California Cannabis Enterprises (CCE). He is an investigator for PTC Therapeutics, Inc., Stoke Therapeutics, Marinus, Ovid and GW Pharmaceuticals. He is supported by Finding a Cure for Epilepsy and Seizures (FACES), the National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Mental Health (NIMH), Multidisciplinary University Research Initiatives (MURI), Centers for Disease Control and Prevention (CDC) and National Science Foundation (NSF). RDT receives research support from Medtronic, Dutch Epilepsy Foundation, 'De Christelijke Vereniging voor de Verpleging van Lijders aan Epilepsie', Netherlands Organization for Health Research and Development (ZonMW) and received consultancy fees as speaker or consultant from Theravance Biopharma, Arvelle, and fees for lectures from Medtronic, UCB and Novartis. JAF receives NYU salary support from the Epilepsy Foundation and for consulting work and/or attending Scientific Advisory Boards on behalf of the Epilepsy Study Consortium for Adamas, Aeonian/Aeovian, Anavex, Arvelle Therapeutics, Inc., Athenen Therapeutics/Carnot Pharma, Axovant, Baergic Bio, Biogen, Biomotiv/Koutif, BioXcel Therapeutics, Blackfynn, Bloom Science, Bridge Valley Ventures, Cavion, Cerebral Therapeutics, Cerevel, Crossject, CuroNZ, Eisai, Eliem Therapeutics, Encoded Therapeutics, Engage Therapeutics, Engrail, Epiminder, Epitel, Equilibre, Fortress Biotech, Greenwich Biosciences, GW Pharma, Idorsia, Ionis, Janssen Pharmaceutica, J&J Pharmaceuticals, Knopp Biosciences, Lundbeck, Marinus, Mend Neuroscience, Merck, NeuCyte, Inc., Neurelis, Neurocrine, Novartis, Otsuka Pharmaceutical Development, Ovid Therapeutics Inc., Passage Bio, Pfizer, Praxis, Redpin, Sage, Shire, SK Life Sciences, Sofinnova, Springworks, Stoke, Sunovion, Supernus, Takeda, UCB Inc., West Therapeutic Development, Xenon, Xeris, Zogenix, Zynerba. JAF has also received research grants from Biogen, Cavion, Eisai, Engage, GW Pharma, Lundbeck, Neurelis, Ovid, Pfizer, SK Life Sciences, Sunovion, UCB, Xenon and Zogenix as well as grants from the Epilepsy Research Foundation, Epilepsy Study Consortium, and NINDS. She is on the editorial board of Lancet Neurology and Neurology Today. She is Chief Medical/Innovation Officer for the Epilepsy Foundation for which NYU receives salary support. She has received travel reimbursement related to research, advisory meetings, or presentation of results at scientific meetings from the Epilepsy Study Consortium, the Epilepsy Foundation, Adamas, Arvelle Therapeutics, Inc., Axovant, Biogen, Blackfynn, Cerevel, Crossject, CuroNz, Eisai, Engage, Idorsia, Lundbeck, NeuCyte, Inc., Neurelis, Novartis, Otsuka, Ovid, Pfizer, Redpin, Sage, SK Life Science, Sunovion, Takeda, UCB, Xenon, Zogenix. DSA, LB and TEW have no conflicts of interest to disclose.

KEY REFERENCES

1. Lamictal. Full prescribing information (last revised October 2020). GlaxoSmithKline, Research Triangle Park, NC 27709, USA. Available at https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Lamictal/pdf/LAMICTAL-PI-MG.PDF (last accessed, January 4, 2021)
2. Saetre E, Abdelnoor M, Amlie JP, Tossebro M, Perucca E, Taubøll E, Anfinson OG, Isojärvi J, Gjerstad L. Cardiac function and antiepileptic drug treatment in the elderly: a comparison between lamotrigine and sustained-release carbamazepine. *Epilepsia* 2009;50(8):1841-9.
3. Svalheim S, Aurlien D, Amlie JP, Gjerstad L, Taubøll E. Signal-averaged and standard electrocardiography in patients with newly diagnosed epilepsy. *Epilepsy Behav.* 2012;25(4):543-5
4. Harmer AR, Valentin JP, Pollard CE. On the relationship between block of the cardiac Na⁺ channel and drug-induced prolongation of the QRS complex. *Br J Pharmacol.* 2011;164(2):260-73
5. Dixon R, Job S, Oliver R, Tompson D, Wright JG, Maltby K, Lorch U, Taubel J. Lamotrigine does not prolong QTc in a thorough QT/QTc study in healthy subjects. *Br J Clin Pharmacol.* 2008;66(3):396-404.
6. Dixon R, Alexander S, Brickel N. Effect of lamotrigine on the PR interval in healthy subjects. *Br J Clin Pharmacol.* 2011;71(6):961-2.
7. Harden C, Tomson T, Gloss D, Buchhalter J, Cross JH, Donner E, French JA, Gil-Nagel A, Hesdorffer DC, Smithson WH, Spitz MC, Walczak TS, Sander JW, Ryvlin P. Practice Guideline Summary: Sudden Unexpected Death in Epilepsy incidence rates and risk factors: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsy Curr.* 2017;17(3):180-187.