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FDA Safety Announcement: Lamotrigine

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On March 31, 2021, the U.S. Food and Drug Administration (FDA) made a safety announcement regarding the antiseizure drug lamotrigine (Lamictal®). This announcement was made in response to findings that therapeutic concentrations of lamotrigine were linked to a higher risk of cardiovascular effects including life-threatening arrhythmias and cardiac arrest. Patients most at risk of experiencing these effects are those who have "clinically important structural or functional heart disorders". This safety announcement also pertains to other drugs in the class that exhibit sodium channel blocking effects, and safety studies are now required for carbamazepine, lacosamide, eslicarbazepine, cenobamate, fosphenytoin, oxcarbazepine, topiramate, phenytoin, zonisamide, and rufinamide to determine if and how they affect the heart.[1]

In response to the FDA, the manufacturer of Lamictal, Glaxo Smith-Kline, updated the package insert in October of 2020 to include two new sections regarding the conduction abnormalities: 5.4: Cardiac Rhythm and Conduction Abnormalities and 12.2: Cardiac Electrophysiology.[2,3]

Based on the currently available data, healthy patients who do not have heart disease should not experience significant changes in ventricular conduction, but they could experience some changes in AV conduction with higher doses.[3] Electrocardiogram (ECG) results have shown mild PR interval prolongation, but there is little evidence to suggest that QT or QRS changes are likely to occur at normal doses. Patients who are currently taking lamotrigine should be counseled not to stop taking their medication without a clinician's guidance. If patients believe they have experienced changes to their heart rate or rhythm, they should contact their provider or go to the emergency department. Providers should use their clinical judgment to determine if changes are necessary to their patients' medication regimen.[1]

In the event of lamotrigine overdose, vital signs should be monitored and basic laboratory studies and an ECG obtained. Signs and symptoms of overdose include nausea and vomiting, somnolence, anorexia, slurred speech, abdominal pain, lethargy, vision disturbances, rash, ataxia, tremor, confusion, agitation, dyskinesia, elevated liver enzymes, and hyperreflexia. With severe toxicity, patients may experience tachycardia and conduction disturbances, oculogyric crisis, hypokalemia, seizures, encephalopathy, rhabdomyolysis, respiratory depression, and coma. Treatment is generally supportive and based on presenting symptoms.[4] If lamotrigine toxicity is suspected, contact the Alabama Poison Information Center at 1-800-222-1222.

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ALABAMA POISON INFORMATION CENTER

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Special Interest Articles

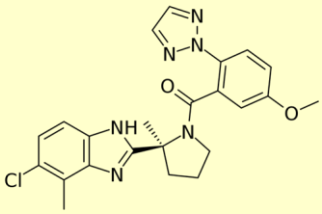
Did you know?

Some snow globes contain ethylene glycol, the same toxic chemical found in antifreeze. If ingested, this substance can cause metabolic acidosis and nephrotoxicity. While the concentration in snow globes is generally lower than in automotive products, these products can still be a serious hazard to small children if sufficient amounts are ingested.

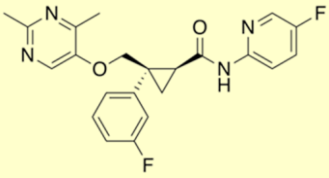
Quviviq® Approved January 10, 2022

By Robert Tooma, PharmD Candidate 2023, Samford University

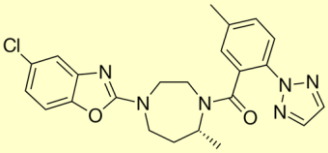
FDA Approved Orexin Antagonists:



Davidorexant (Quviviq)



Lemborexant (Dayvigo)



Suvorexant (Belsomra)

Quviviq (daridorexant) is an oral dual orexin receptor antagonist (DORA) that was approved for the treatment of insomnia (related to sleep onset and/or maintenance), by the U.S. Food and Drug Administration (FDA) in January of 2022. Similar to other marketed orexin receptor antagonist (Belsomra and Dayvigo), this medication blocks the binding of orexin A and orexin B to the OX1R and OX2R receptors. This is crucial in regard to the sleep-wake cycle because orexin is a hypothalamic neuropeptide that helps modulate sleep/wakefulness drive. Unlike other insomnia medications, DORAs promote both non-rapid eye movement (NREM) and rapid eye movement (REM) stages of the sleep cycle which allows them to treat both onset and maintenance insomnia. Additionally, Quviviq is unique from other DORAs because it has a shorter half-life of 8 hours and therefore is marketed as reducing daytime sleepiness. In two phase 3 studies, Quviviq showed significant improvement over placebo in sleep onset, sleep maintenance, and total sleep time while also reducing daytime sleepiness.[1,2]

Quviviq is currently available in 25 mg and 50 mg tablets and is a schedule IV controlled substance due to its potential for abuse and dependance. It is recommended to be taken once daily at night within 30 minutes before bed and with at least 7 hours remaining prior to planned awakening. Due to its mechanism of antagonizing neuropeptide binding, Quviviq comes with various warnings that include CNS depressant effects, worsening depression or suicidal ideation, and complex sleep behaviors (e.g., sleepwalking). The medication is contraindicated for use in patients with narcolepsy.[3]

The adverse effects of Quviviq are primarily associated with its CNS depressant effects and include drowsiness, fatigue, somnolence, headaches, and dizziness. Due to its recent approval, limited data is available on Quviviq overdose and recommendations should be extrapolated from treatment of other DORA medications. Effects in overdose are likely to be an extension of adverse effects. Sedation, respiratory depression, and sleep paralysis are possible. As there is no antidote for DORA toxicity and most effects are self-limiting, general supportive care is recommended.[4] If Quiviq overdose is suspected, contact the Alabama Poison Information Center at 1-800-222-1222.

Table 1: Selected Endpoints Daridorexant vs Placebo at 3 months

Measure	Least Mean Square Difference	95% CI Interval	P-value
50 mg Daily			
LPS	-11.7 minutes	-16.3 to -7.0	<0.0001
WASO	-18.3 minutes	-23.9 to -12.7	<0.0001
IDSIQ	-1.9	-2.9 to -.09	0.0002
25 mg Daily			
LPS	-7.6	-12.3 to -2.9	0.0015
WASO	-11.9	17.5 to - 6.2	<0.0001
IDSIQ	-1.0	-2.0 to 0.01	0.053

LPS: Latency to Persistent Sleep; WASO; Wake After Sleep Onset; IDSIQ: Insomnia Daytime Symptoms Impacts Questionnaire

Yan, C., &; McDermott, M. (2022, February 18). The Role of Daridorexant in the Treatment of Insomnia. Pharmacy Times. Retrieved from https://www.pharmacytimes.com/view/the-role-of-daridorexant-in-the-treatment-of-insomnia

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Carbon Monoxide in Pregnancy

By Lauren Campisi, PharmD, Auburn University

Shepard, B. (2012, September 7). UAB opens new wound clinic with the only emergency hyperbaric chamber in town. UAB News. Retrieved from https://www.uab.edu/news/health/item/2712-uab-opens-new-wound-clinic-with-the-only-emergency-hyperbaric-chamber-in-town

Carbon monoxide (CO) is a gas formed from partial combustion of carbon-containing compounds found in fumes from vehicles, lanterns, stoves, furnaces, boats, generators, and burning wood or coal. A colorless, odorless, and tasteless gas, CO is responsible for over 430 deaths and approximately 50,000 emergency room visits annually.[1] While CO poisoning poses risks in all patient populations, pregnant patients are at increased risk, and extreme caution should be taken due to the potential adverse effects for both the mother and fetus.[2]

After inhalation, CO absorbs quickly and readily then binds to hemoglobin and is transported through the blood as carboxyhemoglobin (COHb). With a 200-250 times greater affinity for hemoglobin than oxygen, CO resides primarily in the blood but is available for distribution into body tissues such as the muscle and brain. The elimination half-life of CO is about 250 minutes which can be significantly reduced to 74-131 minutes on average by treatment with 100% oxygen.[3]

Because CO binds so readily to hemoglobin, oxygen is unable to bind. The unbound oxygen can circulate, and the patient will have adequate partial pressures of oxygen, but there will be decreased arterial oxygenation ultimately leading to inadequate delivery of oxygen to the body's tissues. In addition to impaired oxygen delivery, CO interferes with cellular respiration leading to disrupted oxygen utilization. This impaired oxygen utilization is especially deleterious for high-oxygen demand organs such as the brain and heart.[3]

Symptoms of acute CO poisoning are systemic and nonspecific: dizziness, weakness, headache, chest pain, nausea, vomiting, and altered mental status. The Centers for Disease Control and Prevention lists three red flags for CO poisoning: history of exposure, symptomatic but afebrile, and similar signs and symptoms in multiple patients. A COHb level can be drawn as a diagnostic measure; levels >2% in nonsmokers and >9% in smokers are suggestive of CO poisoning.[4,5]

All patients with suspected CO poisoning of childbearing potential should have a pregnancy test, and if pregnant, a medical toxicologist should be consulted immediately. CO poisoning poses risks to both the mother and fetus due to the hypoxic effects potentially affecting the mother's circulation and therefore the growth and development of the fetus. Case reports of pregnant women with CO poisoning have resulted in various birth defects, miscarriage, stillbirth, preterm birth, low birth weight, learning and behavioral deficits, and neonatal death.[6]

All patients should receive 100% oxygen via a positive-pressure mask or an endotracheal tube to dissociate the COHb, but pregnant patients and patients with higher COHb levels may need hyperbaric oxygen (HBO). For pregnant patients with COHb levels over 5%, a medical toxicologist should be consulted to discuss the potential use of HBO.[7] Maternal COHb does not determine effect on the fetus or fetal demise, but the elimination of CO from the fetus will be extremely delayed and is a major cause of concern for deleterious effects. HBO increases dissolved oxygen amounts in the body tenfold to clear COHb quicker than ambient oxygen.[3]

Other than the low threshold for HBO, pregnant patients should not be treated any differently than other CO poisoning patients. All patients should have neuroimaging and COHb levels checked and should be treated until COHb levels are <5% and all signs and symptoms have resolved. All patients should be counseled on the possibility of delayed neurological complications and given instructions on how to follow up if these symptoms occur. Even in the absence of symptoms, patients should also be advised to have a routine neurological and medical exam two weeks after discharge.[8] If carbon monoxide poisoning is suspected, contact the Alabama Poison Information Center at 1-800-222-1222.

(References on Page 4)

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