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Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance

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Product Name:	Lamictal (lamotrigine)
Pediatric Labeling Approval Date:	May 18, 2015
Application Type/Number:	NDA 020241, 020764, 022251, 022115, 022509
Applicant/Sponsor:	Glaxo Smith Kline
OSE RCM #:	2017-1443

****The drug use data in this review has been cleared by the database vendors. ****

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for lamotrigine in pediatric patients through age <18 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with lamotrigine in pediatric patients.

FDA first approved lamotrigine immediate release (IR) tablets on December 27, 1994. FDA subsequently approved lamotrigine chewable dispersible (CD) tablets on August 24, 1998, and lamotrigine orally disintegrating tablets (ODT) on May 8, 2009. Currently, lamotrigine IR, CD, and ODT are approved for the use in adjunctive therapy for partial onset seizures, primary generalized tonic-clonic seizures, and generalized seizures of Lennox-Gastaut syndrome in patients aged 2 years and older, monotherapy for partial seizures in patients aged 16 years and older, and maintenance treatment of bipolar I disorder in adults.

This pediatric review was stimulated by the most recent lamotrigine pediatric labeling change dated May 18, 2015. The sponsor completed a PREA study on lamotrigine IR, CD, and ODT formulations for the maintenance treatment of bipolar disorder in pediatric patients aged 10 to 17 years. The study failed to show safety and efficacy of lamotrigine for this indication and the product label was updated to reflect the study's findings.

An estimated 134,000 to 139,000 pediatric patients aged 0-16 years received dispensed prescriptions for lamotrigine annually from U.S. outpatient retail pharmacies. DPV analyzed all pediatric postmarketing adverse event reports with a serious outcome for lamotrigine in the FAERS database from May 1, 2014 through March 31, 2018 and identified nine pediatric cases with unlabeled, serious adverse events, of which four cases reported an outcome of death. All four fatal cases lacked information to assess the extent to which lamotrigine contributed to death. Of the five remaining unlabeled and serious adverse event cases, no specific pattern of adverse events was noted. The five nonfatal cases reported unlabeled events of serotonin syndrome (n=1), tubulointerstitial nephritis (TIN) with uveitis and Cogan syndrome (n=1), and one literature report describing cases of oculogyric crisis (n=3) in association with lamotrigine use.

There is no evidence of pediatric safety concerns with lamotrigine that warrant a labeling update and DPV recommends no regulatory action at this time. DPV will continue monitoring for all adverse events associated with the use of lamotrigine, including serotonin syndrome, TIN, and oculogyric crisis.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for lamotrigine in pediatric patients through age <18 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with lamotrigine in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

FDA first approved lamotrigine immediate release (IR) tablets on December 27, 1994. FDA subsequently approved lamotrigine chewable dispersible (CD) tablets on August 24, 1998, and lamotrigine orally disintegrating tablets (ODT) on May 8, 2009. Currently, lamotrigine IR, CD, and ODT are approved for the use in adjunctive therapy for partial onset seizures, primary generalized tonic-clonic seizures, and generalized seizures of Lennox-Gastaut syndrome in patients aged 2 years and older, monotherapy for partial seizures in patients aged 16 years and older, and maintenance treatment of bipolar I disorder in adults.

FDA approved lamotrigine extended release (XR) on May 29, 2009, for the use in adjunctive therapy for partial onset seizures in patients 13 years of age or older. Subsequently, lamotrigine XR formulation was approved for adjunctive therapy for primary generalized tonic-clonic seizures in patients 13 years of age or older, and for monotherapy of partial seizures in patients 13 years of age and older. Lamotrigine IR, CD, ODT, and XR formulations have different indications and are approved for different age groups. Appendix A summarizes the United States (U.S.) approval history of all lamotrigine formulations.

Lamotrigine IR and CD were approved for the maintenance treatment of bipolar disorder in adult patients on June 20, 2003.[1,2]

1.1.1 Pediatric Bipolar Disorder Study (Trial NCT00723450)

This pediatric review was stimulated by the pediatric labeling change dated May 18, 2015. NCT00723450 was a multicenter, placebo-controlled, double-blind randomized withdrawal trial of lamotrigine in subjects 10 to 17 years old who were diagnosed with bipolar I disorder. The trial evaluated the efficacy, safety, and tolerability of lamotrigine as add-on therapy compared to maintenance mono- or dual-therapy alone. The study compared efficacy of lamotrigine versus placebo in delaying the time to occurrence of a bipolar event (TOBE) in subjects who previously responded to open-label lamotrigine treatment added to their conventional mono- or dual-bipolar therapy. The result of the primary analysis for the overall population of 10 to17-year-old patients did not reach statistical significance. NCT00723450 fulfilled the requirement for pediatric studies under PREA. The efficacy and safety data from this study are described in the PEDIATRIC USE section of labeling. [3,4]

1.1.2 Pediatric Advisory Committee and Pediatric Safety Reviews

On September 30, 2008, DPV completed a review on lamotrigine for the 1-year period following the approval of pediatric exclusivity for the treatment of partial seizures on February 14, 2007. The review did not reveal any new safety concerns associated with the use of lamotrigine in children. The DPV review was presented to the Pediatric Advisory Committee (PAC) on November 18, 2008. The PAC agreed with the DPV recommendation for standard, ongoing postmarketing safety monitoring.[5,6]

DPV performed a PREA review on lamotrigine XR on May 29, 2009, that was stimulated by the approved indication for adjunctive therapy of partial onset seizures and primary generalized tonic-clonic seizures in patients 13 years of age and older. DPV opened a tracked safety issue (TSI) based on the identification of one case of neonatal cyanosis associated with lamotrigine exposure via breastmilk in this review. The review did not identify any other new safety concerns.[7] The DPV review was presented to the PAC on December 7, 2010. The PAC expressed concern regarding the lack of lactation data in the label of all lamotrigine formulations and advised FDA to revise the labeling to include lactation data from the literature and ongoing studies and to provide a follow-up in one year.[8]

DPV completed a postmarketing safety review on December 6, 2010, and identified 18 cases reporting adverse events in infants following exposure to lamotrigine via breast milk. DPV recommended updating the label to incorporate available data on postmarketing cases involving infants exposed to lamotrigine via breast milk.[9] On August 1, 2012, labeling changes were made to the *Pregnancy*, *Nursing Mothers* and PATIENT COUNSELING INFORMATION Section, and Medication Guide. The label changes described presence of lamotrigine in breast milk and adverse events such as apnea, drowsiness, and poor sucking in breast-fed infants. FDA closed the TSI on neonatal cyanosis after lamotrigine exposure via breast milk on March 1, 2013.[10]

On November 19, 2012, DPV completed a PREA review on lamotrigine XR triggered by the expanded indication of monotherapy treatment of partial seizures in patients 13 years of age and older. The review did not identify any new safety concerns.[11] The DPV review was presented to the PAC on March 14, 2013. PAC recommended standard, ongoing monitoring for adverse events and recommended updating the WARNINGS AND PRECAUTIONS Section of the lamotrigine XR label to include information about breathing problems in infants who are breastfeeding from mothers who are on lamotrigine XR.[12] In a postmarketing review dated December 29, 2014, DPV did not identify safety concerns regarding serious adverse events in neonates exposed to lamotrigine via human milk from lactating mothers. DPV recommended continuing routine pharmacovigilance.[13]

1.2 LABELING [1,2]

1.2.1 Dosing and Administration

Lamotrigine is available in the following dosage forms:

- NDA 020241: oral tablet (25 mg, 100 mg, 150 mg, 200 mg)
- NDA 020764: chewable dispersible (CD) tablet (2 mg, 5 mg, 25 mg)
- NDA 022251: orally disintegrating (ODT) tablet (25 mg, 50 mg, 100 mg, 200 mg)
- NDA 022115: extended release (XR) tablet (25 mg, 50 mg, 100 mg, 200 mg, 250 mg, 300 mg)
- NDA 022509: extended release (XR) tablet (25 mg, 50 mg, 100 mg, 200 mg)

Dosing is typically initiated at 25-50 mg daily and titrated up to a maintenance dose of 100 to 500 mg daily for adult patients. For pediatric patients, 0.15 to 0.6 mg/kg/day is recommended up to maximum dose of 5-15 mg/kg/day. Pharmacokinetics and dosing are altered based on concomitant medications and drug interactions.

1.2.2 Highlights and Relevant Labeled Safety Issues

BOXED WARNING: SERIOUS SKIN RASHES

- Cases of life-threatening serious rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis, and/or rash-related death have been caused by lamotrigine. The rate of serious rash is greater in pediatric patients than in adults. Additional factors that may increase the risk of rash include:
  - coadministration with valproate.
  - exceeding recommended initial dose of LAMICTAL.
  - exceeding recommended dose escalation for LAMICTAL. (5.1)
- Benign rashes are also caused by lamotrigine; however, it is not possible to predict which rashes will prove to be serious or life threatening. LAMICTAL should be discontinued at the first sign of rash, unless the rash is clearly not drug related. (5.1)

CONTRAINDICATIONS

Hypersensitivity to the drug or its ingredients. (Boxed Warning, 4)

WARNINGS AND PRECAUTIONS

- Life-threatening serious rash and/or rash-related death: Discontinue at the first sign of rash, unless the rash is clearly not drug related. (Boxed Warning, 5.1)
- Multiorgan hypersensitivity reactions, also known as drug reaction with eosinophilia and systemic symptoms (DRESS), have occurred with LAMICTAL. Some have been fatal or life threatening. DRESS typically, although not exclusively, presents with fever, rash, and/or lymphadenopathy in association with other organ system involvement, such as hepatitis, nephritis, hematologic abnormalities, myocarditis, or myositis, sometimes resembling an acute viral infection. Eosinophilia is often present. This disorder is variable in its expression, and other organ systems not noted here may be involved.

Fatalities associated with acute multiorgan failure and various degrees of hepatic failure have been reported in 2 of 3,796 adult patients and 4 of 2,435 pediatric patients who received LAMICTAL in epilepsy clinical trials. Rare fatalities from multiorgan failure have also been reported in postmarketing use.
Isolated liver failure without rash or involvement of other organs has also been reported with LAMICTAL.
It is important to note that early manifestations of hypersensitivity (e.g., fever, lymphadenopathy) may be present even though a rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. LAMICTAL should be discontinued if an alternative etiology for the signs or symptoms cannot be established.
Prior to initiation of treatment with LAMICTAL, the patient should be instructed that a rash or other signs or symptoms of hypersensitivity (e.g., fever, lymphadenopathy) may herald a serious medical event and that the patient should report any such occurrence to a healthcare provider immediately. (5.2)

- Blood dyscrasias (e.g., neutropenia, thrombocytopenia, pancytopenia): May occur, either with or without an associated hypersensitivity syndrome. Monitor for signs of anemia, unexpected infection, or bleeding. (5.3)
- Suicidal behavior and ideation: Monitor for suicidal thoughts or behaviors. (5.4)
- Aseptic meningitis: Monitor for signs of meningitis. (5.5)

ADVERSE REACTIONS

Epilepsy: Most common adverse reactions (incidence ≥10%) in adults were dizziness, headache, diplopia, ataxia, nausea, blurred vision, somnolence, rhinitis, pharyngitis, and rash. Additional adverse reactions (incidence ≥10%) reported in children included vomiting, infection, fever, accidental injury, diarrhea, abdominal pain, and tremor. (6.1)

Bipolar disorder: Most common adverse reactions (incidence >5%) in adults were nausea, insomnia, somnolence, back pain, fatigue, rash, rhinitis, abdominal pain, and xerostomia. (6.1)

Nervous System: Amnesia, depression, agitation, emotional lability, dyspraxia, abnormal thoughts, dream abnormality, hypoesthesia. (6.1)

Special Senses
Rare: Deafness, lacrimation disorder, oscillopsia, parosmia, ptosis, strabismus, taste loss, uveitis, visual field defect. (6.2)

Nervous System
Infrequent: Akathisia, apathy, aphasia, central nervous system depression, depersonalization, dysarthria, dyskinesia, euphoria, hallucinations, hostility, hyperkinesia, hypertonia, libido decreased, memory decrease, mind racing, movement disorder, myoclonus, panic attack, paranoid reaction, personality disorder, psychosis, sleep disorder, stupor, suicidal ideation.
Rare: Choreoathetosis, delirium, delusions, dysphoria, dystonia, extrapyramidal syndrome, faintness, grand mal convulsions, hemiplegia, hyperalgesia, hyperesthesia,

hypokinesia, hypotonia, manic depression reaction, muscle spasm, neuralgia, neurosis, paralysis, peripheral neuritis. (6.2)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data may cause fetal harm. (8.1)
- Hepatic impairment: Dosage adjustments required in patients with moderate and severe liver impairment. (2.1, 8.6)
- Renal impairment: Reduced maintenance doses may be effective for patients with significant renal impairment. (2.1, 8.7)
- Pediatric Use (Bipolar Disorder)
  Safety and efficacy of LAMICTAL for the maintenance treatment of bipolar disorder were not established in a double-blind, randomized withdrawal, placebo-controlled trial that evaluated 301 pediatric patients aged 10 to 17 years with a current manic/hypomanic, depressed, or mixed mood episode as defined by DSM-IV-TR. In the randomized phase of the trial, adverse reactions that occurred in at least 5% of patients taking LAMICTAL (n = 87) and were twice as common compared to patients taking placebo (n = 86) were influenza (LAMICTAL 8%, placebo 2%), oropharyngeal pain (LAMICTAL 8%, placebo 2%), vomiting (LAMICTAL 6%, placebo 2%), contact dermatitis (LAMICTAL 5%, placebo 2%), upper abdominal pain (LAMICTAL 5%, placebo 1%), and suicidal ideation (LAMICTAL 5%, placebo 0%).

2 METHODS AND MATERIALS

2.1 FDA ADVERSE EVENT REPORTING SYSTEM SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 1. See Appendix B for a description of the FAERS database.

Table 1. FAERS Search Strategy	
Date of search	April 27, 2018
Time period of search	May 1, 2014* - March 31, 2018
Search type	Drug Safety Analytics Dashboard (DSAD) Quick Query
Product terms	Product active ingredient: lamotrigine
MedDRA search terms (Version 20.1)	All PT terms
Search parameters	All ages, all outcomes, worldwide
** May 1, 2014 is the date 1 year prior to the last pediatric labeling change, which occurred on May 18, 2015.*	

2.2 DRUG UTILIZATION

We used proprietary drug utilization databases available to FDA to conduct this analysis. Detailed database descriptions are provided in Appendix C.

2.2.1 Data Source Used

IQVIA National Sales Perspectives™ (NSP) database was used to obtain the nationally estimated number of bottles sold for lamotrigine from the manufacturer to all U.S. channels of distribution in 2017. The sales distribution data represent the amount of product sold from manufacturers to pharmacies and other settings of care; it does not reflect what is being sold to or administered to patients directly.

IQVIA, Total Patient Tracker™ (TPT) database was used to provide the nationally estimated number of patients, stratified by patient age, who received a dispensed prescription for lamotrigine from U.S. outpatient retail pharmacy settings from the 12-month period ending March 2015 through the 12-month period ending March 2018.

3 RESULTS

3.1 FDA ADVERSE EVENT REPORTING SYSTEM SEARCH

3.1.1 Total Number of FAERS Reports by Age

Table 2 presents the number of adult and pediatric FAERS reports from May 1, 2014, to March 31, 2018 with lamotrigine.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA from May 1, 2014 to March 31, 2018 with Lamotrigine

	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥17 years)	8009 (4002)	7052 (3119)	1602 (1242)
Pediatrics (0 - <17 years)	1314 (404)	1247 **(346)**‡	58 (21)

* May include duplicates and transplacental exposures, and have not been assessed for causality

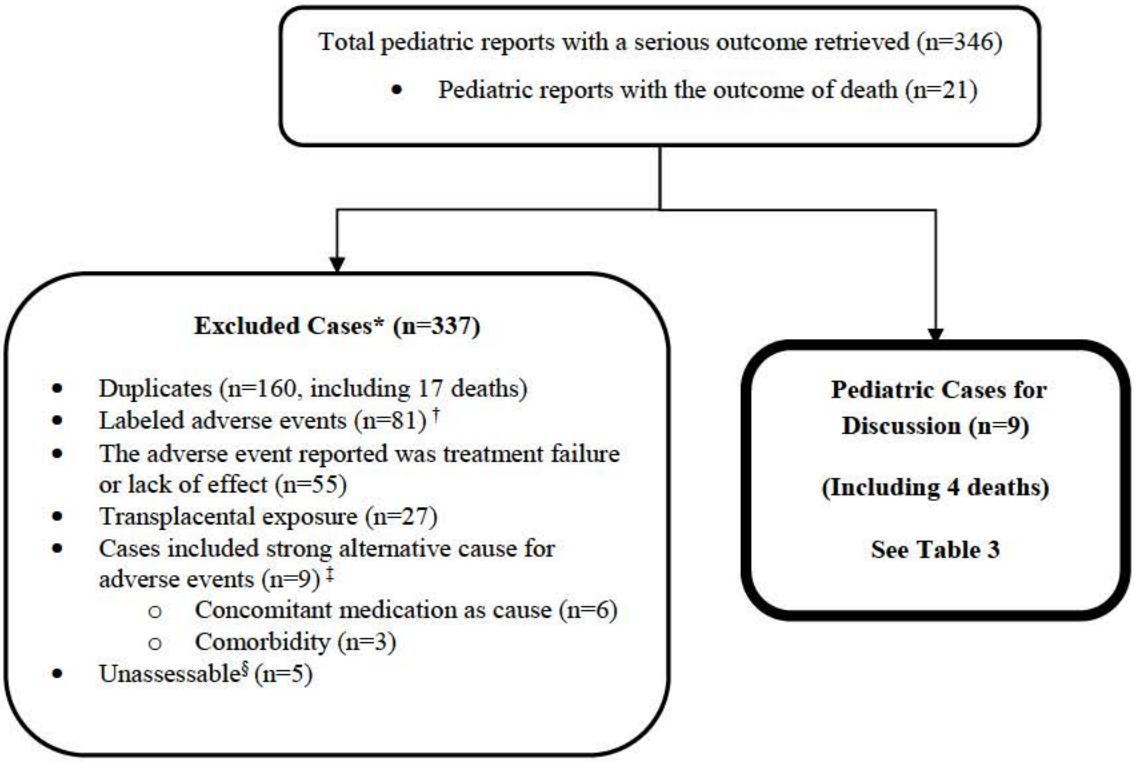
† For the purposes of this review, the following outcomes qualify as serious: death, life- threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

‡ See Figure 1

3.1.2 Selection of Serious Pediatric Cases in FAERS

Our FAERS search retrieved 346 U.S. serious pediatric reports from May 1, 2014 to March 31, 2018. Our review focuses on U.S. FAERS pediatric reports reporting death and cases reporting serious unlabeled adverse events. Figure 1 presents the specific selection of cases for discussion in **Section 3.1.3.**

Figure 1. Selection of Serious U.S. Pediatric Cases with Lamotrigine



* DPV reviewed these cases, but they were excluded from further discussion for the reasons listed above

† Labeled adverse events include rash (n=35), neuropsychiatric disturbances (n=20), hypersensitivity (n=6), suicidal behavior and ideation (n=6), gastrointestinal adverse events (n=4), blood dyscrasias (n=3), psychiatric disorders (n=2), eye disorders (n=2), lactation related adverse event (n=1), nervous system disorder (n=1), seizure due to overdose (n=1)

‡ Nine serious pediatric reports described strong alternative causes for the adverse event. Strong alternative causes included adverse events caused by concomitant medications (n=6; neuroleptic malignant syndrome caused by haloperidol and risperidone n=2, increased prolactin from aripiprazole n=1, edema and discharge related to baclofen catheter pump n=3) and comorbid conditions (n=3; allergic colitis flare from comorbid colitis n=1, seizure leading to asystole n=1, low potassium causing QT prolongation n=1).

§ Unassessable: Case cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome) or the information is contradictory or information provided in the case cannot be supplemented or verified.

We identified 346 pediatric reports with serious outcomes, of which 160 were duplicates. Eighty-one serious pediatric reports described labeled events. DPV reviewed these cases and noted no increase in severity of adverse events.

Of the remaining 105 reports, 27 described transplacental exposure and 55 described treatment failure or lack of effect as the adverse event. Nine reports described strong alternative causes for the adverse event. Five serious pediatric reports lacked information to make a meaningful causality analysis.

3.1.3 Characteristics of Pediatric Cases

Appendix D contains a line listing of the nine pediatric cases discussed in this review.

Table 3 summarizes the nine FAERS cases in U.S. pediatric patients with lamotrigine reporting an unlabeled serious outcome received by FDA from May 1, 2014 to March 31, 2018.

Table 3. Characteristics of the FAERS U.S. Serious Pediatric Cases with lamotrigine Received by FDA from May 1, 2014 to March 31, 2018 (N=9)	
Age	
1 month - <2 years	1
2 - < 6 years	1
6 - <12 years	3
12 - < 18 years	4
Sex	
Male	5
Female	4
Reported reason for use	
Seizures	4
Accidental	1
Not Reported	4
Serious outcome*	
Death	4
Hospitalization	3
Other	3
* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events. Cases may have more than one outcome.	

3.2 SUMMARY OF FATAL PEDIATRIC CASES (N=4)

We retrieved four cases with lamotrigine reporting a fatal outcome. All cases were reported from literature sources. One case (FAERS Case #11913398) reported an 8-year-old boy with accidental ingestion of lamotrigine with multiple co-ingested products and two cases (FAERS Cases #13092260, 14241798) reported 16-year-old girls with completed suicides after ingestion of lamotrigine with multiple co-ingested medications. One case (FAERS Case #14690907) reported a 16-year-old boy who took lamotrigine and multiple co-ingested medications for unknown indication(s) and developed multisystem dysfunction for which he required intensive care including extracorporeal membrane oxygenation; he did not recover and died at an unspecified time and it is unknown if this death case represents a completed suicide. Three cases reported completion of autopsies, of which one case reported postmortem drug levels for lamotrigine and co-ingested medications; no other results from autopsy were revealed. All three cases reported lamotrigine to be least likely of the ingested agents to contribute to death on cause rank analysis based on autopsy findings. No other information is available on the four death cases.

Reviewer comment: Suicidality is labeled within the WARNINGS AND PRECAUTIONS Section 5.4 of the lamotrigine label.[1] *All cases with fatal outcomes derived from toxico-surveillance*

periodic reports from toxicology and poison control data systems; the reports contained patient-level demographic and outcomes data, but lacked a narrative history including information on chronicity and temporality of lamotrigine to other medications, comorbid conditions, and information on laboratory evaluations. Furthermore, there is insufficient information to determine if lamotrigine is a prescribed medication in these cases. It is not possible to form a meaningful causality analysis in the absence of this information.

3.3 SUMMARY OF NON-FATAL PEDIATRIC U.S. SERIOUS CASES (N=5)

We identified five nonfatal cases reporting unlabeled events of serotonin syndrome (n=1); tubulointerstitial nephritis (TIN) with uveitis and Cogan syndrome (n=1); and one literature report describing cases of oculogyric crisis (n=3) in association with lamotrigine use. The five cases are described below.

3.3.1 Serotonin Syndrome (N=1)

FAERS # 10785303, MCN: PHHY2015US015169, 2015: a literature[14] article reported a 1-year-old girl who had a witnessed ingestion of an unknown quantity of her parent's lamotrigine and experienced serotonin syndrome. The patient had no significant medical history and she took no other medications. She presented with agitation, crying, and intermittent myoclonus of extremities with alternating hypotonia and she had inducible clonus on exam. Her serum lamotrigine level was 18 mg/L at 8 hours after ingestion and 11.8 mg/L at 19 hours after ingestion. The girl was diagnosed with serotonin syndrome; she was treated with lorazepam and ondansetron and discharged home after 19 hours.

Reviewer's comment: This child's symptoms met the Hunter Serotonin Toxicity Criteria of agitation, diaphoresis, and inducible clonus. Appendix E describes the Hunter Serotonin Toxicity Criteria.[15] No other medications were identified in the case. There are no definitive studies to establish the mechanism of how lamotrigine may cause serotonin syndrome. Some laboratory studies suggest a possible biologic plausibility through the inhibition of reuptake of 5-HT to create a serotonergic effect.[16]

This case may represent a cluster of known adverse events as a result of an overdose as lamotrigine is labeled for agitation, myoclonus, and hypotonia in ADVERSE REACTIONS Section 6.1 and 6.2.[1] Furthermore, it is notable that the case reports overdose in a patient whose age is outside the normal indication for lamotrigine. The neurobiology and pharmacokinetics of an infant varies significantly from children and adults, therefore, this patient's reaction to lamotrigine cannot be used to make inference about safety in labeled patient population.

For completeness, we searched the FAERS database for cases of serotonin syndrome in the adult population. We retrieved 142 reports of which 104 were duplicates, 6 lacked sufficient information to form a causality assessment, and 28 cases reported serotonergic agents and

monoamine oxidase inhibitors as concomitant medications. None of the remaining four cases met the case definition for serotonin syndrome. We also searched the medical literature and did not identify any additional cases. Appendix F describes the FAERS and literature search strategies.

3.3.1 Tubulointerstitial Nephritis (N=1)

FAERS # 11870341, MCN: US-TARO PHARMACEUTICALS USA.,INC-2015SUN02309, 2015: a literature[17] article reported a 16-year-old boy with a history of traumatic brain injury and seizures developed TIN and uveitis-atypical Cogan Syndrome with lamotrigine use. The patient had an increase in lamotrigine dose secondary to breakthrough seizures and several days later he presented with facial edema, rash, and back pain. Laboratory evaluation was notable for elevated serum creatinine and eosinophils and urine positive for β2 microglobulin. Antinuclear antibodies (ab), antineutrophil cytoplasmic ab, angiotensin-converting enzyme, and complement levels were normal; evaluations for infections such as hepatitis B, hepatitis C, human herpes virus-6, chlamydia, Epstein-Barr virus, and urinary tract infections were normal. Renal biopsy showed acute granulomatous TIN. Diagnostic imaging studies including renal ultrasound and colonoscopy were normal. The patient was suspected to have drug reaction with eosinophilia and systemic symptoms (DRESS); his lamotrigine treatment was suspended and he received pulse-dosed intravenous steroids. The patient was discharged from the hospital at an unspecified time with lorazepam and prednisone. After discharge, the patient developed bilateral anterior uveitis and was diagnosed with lamotrigine-induced tubulointerstitial nephritis and uveitis (TINU) that was treated with prednisolone and cyclopentolate. Two months later, he developed branch retinal artery occlusion in the right eye and bilateral ocular hypertension that was treated with timolol-brimonidine and dorzolamide. Magnetic resonance imaging (MRI) with angiography and venography showed stable mild cerebellar ectopia. Other diagnostic tests including echocardiogram, electrocardiogram, and hypercoagulability blood panel were normal. The patient's anterior uveitis persisted after 4 months despite increased frequency of topical prednisolone, difluprednate, and oral prednisone dosing. The patient then developed central serous retinopathy in the right eye, which led to discontinuation of prednisone therapy. He was later diagnosed with posterior scleritis of the right eye and received a sub-tenon triamcinolone injection and methotrexate treatment; methotrexate was discontinued due to gastrointestinal symptoms and prednisone was restarted. A week later, the patient's vision was stable but he developed sensorineural hearing loss, nausea, vomiting and dizziness. Brain MRI showed "infratentorial foci of vasogenic edema and perivascular, subcortical, and bilateral cochlear enhancement" suggestive of an autoimmune vasculitis. He received transtympanic membrane dexamethasone injections, infliximab infusions, and he was fitted for hearing aids. After 9 months, the patient had mild systemic improvement, stable vision, normal intraocular pressure, and "preserved renal function," but his hearing remained limited.

Reviewer's comment: Lamotrigine is labeled for uveitis and deafness within the ADVERSE REACTIONS Section 6.2 of the product label and nephritis in association with DRESS in

WARNINGS AND PRECAUTIONS Section 5.2, but it is not labeled for TIN.[1] TINU and Cogan's syndrome are distinct and rare conditions. TINU describes a rare autoimmune syndrome mediated by humoral and cellular mechanisms. Cogan syndrome is a chronic inflammatory disorder involving vestibuloauditory and ocular systems with associated systemic vasculitis; autoimmunity is also implicated in Cogan syndrome pathophysiology.[18] The patient's symptoms and findings are consistent with TINU and Cogan syndrome, but many other autoimmune, inflammatory, and infectious conditions (e.g., sarcoidosis, Sjogren's syndrome, Behcet's disease, tuberculosis, and syphilis) may elicit similar symptoms. The initial renal biopsy revealed granulomatous interstitial nephritis that would favor the diagnosis of sarcoid and other granulomatous diseases instead of TINU, but the case does not offer explicit details on this biopsy or describe repeat renal biopsies. Furthermore, the laboratory and diagnostic evaluations only partially rule out other differential diagnoses as the cause for symptoms. In addition, the events started after lamotrigine exposure, however, lamotrigine therapy was discontinued after his first diagnosis of DRESS and the case does not specify if lamotrigine was restarted before he developed more adverse events.

While it is unusual for a patient to experience two rare diseases, the medical literature has case reports of TINU with Cogan syndrome, TINU with hearing loss, and Cogan syndrome with renal involvement.[18-21] However, these case reports do not associate TINU and Cogan syndrome with lamotrigine or other drug use; it is possible this case does not represent an adverse drug reaction, but rather a rare or under-recognized combination of syndromes provoked by a shared autoimmune mechanism. Furthermore, the case is confounded by concomitant use of steroids, which is associated with the development of central serous retinopathy, and methotrexate, which is labeled for renal toxicity in ADVERSE REACTIONS Section of the product label.[22,23] Causality analysis is difficult due to weak temporality, lack of details including dechallenge and rechallenge trials, patient baseline laboratory values, and clinical conditions.

For completeness, we searched the FAERS database for cases of TIN in the adult population. We retrieved 36 reports of which 14 were duplicates and 16 lacked sufficient information to form a causality assessment. Of the six remaining cases, five cases described TIN in the setting of suspected DRESS. Nephritis is a presenting symptom in some cases of DRESS and nephritis in association with DRESS is labeled in the WARNINGS AND PRECAUTIONS Section 5.2 of the lamotrigine product label.[1] This is a plausible mechanism through which lamotrigine causes TIN. The remaining case was reported from the literature and described a 19-year-old woman who developed TINU while on lamotrigine therapy for bipolar disorder; the case was notable for weakly positive antinuclear antibody, "abnormal serum creatinine," and elevated β2 microglobulin.[24] Lack of information precluded a strong causality assessment in this case as there was no renal biopsy performed and the case lacked information such as specific laboratory evaluations, concomitant medications, comorbid conditions, dechallenge and rechallenge trials, and temporal relationships between lamotrigine use and adverse events. We also searched the

medical literature and did not identify any additional cases. Appendix F describes the FAERS and literature search strategies.

3.3.2 Oculogyric Crisis (N=3)

FAERS # 14560628, MCN: US-ALKEM LABORATORIES LIMITED-US-ALKEM-2018-00682, 2018: a literature[25] article reported a 3-year-old boy with a medical history of atypical absence and generalized tonic-clonic seizures developed oculogyric crisis following a lamotrigine dose increase to 7.8 mg/kg/day. The patient's comorbid conditions included x-linked ichthyosis, left cerebral hemisphere microgyria, and right hemiparesis. He developed sustained upward deviation of both eyes that lasted up to one minute. Concomitant medication included clonazepam. The episodes were associated with "sleepiness" and he experienced these episodes once per day for one month. The patient's symptoms resolved following lamotrigine dose reduction to 4 mg/kg/day. The patient's lamotrigine plasma concentrations during and after dose increase were not reported.

FAERS # 14560626, MCN: US-ALKEM LABORATORIES LIMITED-US-ALKEM-2018-00674, 2018: a literature[25] article reported a 10-year-old girl with a medical history of juvenile Tay-Sachs disease and generalized tonic-clonic seizures who developed oculogyric crisis following a dose increase of lamotrigine from 22 mg/kg/day to 25 mg/kg/day. Concomitant medication included clonazepam. She developed sustained upward deviation of both eyes occurring multiple times per day and lasting 2 to 3 hours per episodes for a total of 3 days and symptoms were associated with tremulousness and irritability. Continuous electroencephalography (EEG) monitoring reported the oculogyric events occurred without corresponding electrographic activity. The patient's lamotrigine plasma concentration was 15.8 mcg/mL during the dose increase and 8.5 mcg/mL after dose reduction. The patient's symptoms resolved following dose reduction of lamotrigine.

FAERS # 14560635, MCN: US-ALKEM LABORATORIES LIMITED-US-ALKEM-2018-00683, 2018: a literature[25] article reported an 11-year-old boy with a medical history of absence seizures developed oculogyric crisis following a lamotrigine dose increase from 5.5 mg/kg/day to 7 mg/kg/day. Concomitant medication included valproate. He developed sustained upward deviation of both eyes lasting up to 4 seconds; this occurred multiple times per day for 3 months and symptoms were associated with staring and excessive blinking. Continuous EEG monitoring captured two of the oculogyric episodes but found no electrographic correlates; the patient's lamotrigine plasma concentration during dose increase was 9.3 mcg/ml. The patient's symptoms resolved following a lamotrigine dose reduction.

Reviewers comment: Oculogyric crisis is an acute dystonic reaction involving the extraocular muscles and involves involuntary bilateral eye deviation lasting seconds to hours. Medications are known triggers of oculogyric crisis and neuroleptic products are most commonly implicated, however, other medications including benzodiazepines and anticholinergics have been involved.[26] Oculogyric crisis is also associated with other conditions such as head trauma,

seizures, and multiple sclerosis.[27] Oculogyric crisis is not a common feature of X-linked ichthyosis or Tay-Sachs disease. The temporal association and the positive dechallenge reported in all three cases suggests a causal association between lamotrigine and oculogyric events is possible. However, it is not possible to definitively assess the extent to which lamotrigine contributed to the events in two of the cases as they reported concomitant medications (valproate n=1, clonazepam n=2) but did not describe the action taken with the concomitant medications. Clonazepam and valproate are not labeled for oculogyric crisis.[28,29] Notably, two of the cases of oculogyric crisis reported lamotrigine plasma concentrations that were not in the toxic range, while the third case did not report plasma concentrations.[30] Two of the cases reported EEG findings that rule out seizure as a cause of oculogyric crisis, but all cases lacked information about baseline seizure characteristics and control, socio-developmental history, and diagnostic and laboratory evaluations to rule out other etiologies such as structural brain lesions, infections, or behavioral processes.

For completeness, we searched the FAERS database for additional cases of oculogyric crisis in the adult population. We retrieved 17 reports of which 13 reports were duplicates and one report involved concomitant medications aripiprazole and risperidone that are associated with oculogyric crisis.[31,32] Two cases lacked sufficient information to form a causality assessment. One case derived from the same literature article reporting the three pediatric cases. The case described a 25-year-old man with sickle cell disease who took lamotrigine for the treatment of seizures and developed oculogyric crisis after accidental lamotrigine overdose of 23.5mg/kg/day the previous day. His lamotrigine level during oculogyric crisis was 16.5 mcg/mL. His symptoms resolved after return to his original lamotrigine dose. The case also lacked information about baseline seizure characteristic and control, comorbid conditions, and diagnostic evaluations for causality assessment. We also searched the medical literature and did not identify any additional cases. Appendix F describes the FAERS and literature search strategies.

3.4 DRUG UTILIZATION

3.4.1 Determining Settings of Care

In 2017, approximately 83% of all lamotrigine products were distributed to U.S. outpatient retail pharmacy settings, followed by 10% to non-retail pharmacies, and 7% to mail-order/specialty pharmacies.[1] Accordingly, we focused our efforts on the long-term care and outpatient retail settings. Data from mail-order/specialty pharmacy settings were not included.

3.4.2 Patient Data

Utilization of lamotrigine was also assessed using a proprietary drug utilization database available to the Agency (See Appendix C for database description) to provide context for the

[1] IQVIA National Sales Perspectives™ (NSP) Database. 2017. Extracted August 2018. File: 2017-1443 NSP lamotrigine.xlsx.

adverse event reports. For the 12-month period ending March 2015, an estimated 139,000 pediatric patients aged 0-16 years (8% of total patients) received dispensed prescriptions for lamotrigine from U.S. outpatient retail pharmacies; utilization decreased to an estimated 134,000 patients (6% of total patients) for the 12-month period ending March 2018.[2]

4 DISCUSSION

DPV analyzed all pediatric postmarketing adverse event reports with a serious outcome for lamotrigine in the FAERS database from May 1, 2014 through March 31, 2018. The nine serious cases in this review include four cases with an outcome of death and five cases of nonfatal serious adverse events. Of the four death cases, three were completed suicides involving co-ingestion of multiple medications including lamotrigine, and autopsy findings suggested lamotrigine was the least likely ingested medication to have contributed to death. The fourth death case involved co-ingestion of multiple drugs without reporter cause rank analysis for lamotrigine. We cannot determine whether lamotrigine is a prescribed medication in these cases. All fatal cases lacked sufficient information to assess the extent to which lamotrigine contributed to the outcome of death.

Of the five serious and unlabeled adverse event cases, no specific pattern of adverse events was noted. There was a single report of serotonin syndrome in a patient with therapeutic levels of lamotrigine, and TINU with Cogan syndrome in a patient with a complex medical course confounded by concomitant medications and limited history. Three cases reported from a singular literature article described oculogyric crisis, but all cases lacked additional details to perform a thorough causality assessment. In addition, a search of the FAERS database for adult cases of TIN, serotonin syndrome, or oculogyric crisis reported in association with lamotrigine resulted in the identification of five cases reporting TIN in the setting of eosinophilia or DRESS syndrome, one case reporting TINU, no cases of serotonin syndrome, and one case of oculogyric crisis; all adult cases lacked additional information to perform a substantial causality assessment.

An estimated 134,000 to 139,000 pediatric patients aged 0-16 years received dispensed prescriptions for lamotrigine annually from U.S. outpatient retail pharmacies. In the setting of high pediatric lamotrigine utilization, a singular case of serotonin syndrome and limited cases of TIN and oculogyric crisis do not represent a safety signal at this time.

5 CONCLUSION

DPV analyzed all pediatric postmarketing adverse event reports with a serious outcome for lamotrigine in the FAERS database from May 1, 2014 through March 31, 2018. There is no evidence of pediatric safety concerns with lamotrigine that warrant a labeling update at this time.

[2] IQVIA Total Patient Tracker™ (TPT) Database. 2015-2018. Extracted July 2018. File: 2017-1443 TPT Lamotrigine.xlsx.

6 RECOMMENDATIONS

DPV recommends no regulatory action and will continue monitoring for all adverse events associated with the use of lamotrigine, including serotonin syndrome, TIN, and oculogyric crisis.

7 REFERENCES

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8 APPENDICES

8.1 APPENDIX A. U.S. LABELING HISTORY OF LAMOTRIGINE

Appendix A. U.S. Approval History of Lamotrigine					
Date	**Product Formulation***				**Indication Change(s)**
	IR	CD	ODT	XR	
12/27/1994	X				Adjunctive treatment of partial seizures in adult patients
8/24/1998	X	X			Adjunctive treatment of Lennox-Gastaut syndrome in patients ≥ 2 years of age
12/14/1998	X	X			Monotherapy for partial seizures in patients ≥ 16 years of age
1/17/2003	X	X			Adjunctive therapy for partial seizures in patients ≥ 2 years of age
6/20/2003	X	X			Maintenance treatment of bipolar disorder in patients ≥18 years of age
9/22/2006	X	X			Adjunctive therapy for primary generalized tonic-clonic seizures in patients ≥ 2 years of age
5/8/2009	X	X	X		Adjunctive therapy for partial seizures in pediatric patients 1-24 months was not established safe and effective
5/29/2009				X	Adjunctive therapy for partial onset seizures in patients ≥ 13 years of age
1/29/2010				X	Adjunctive therapy for primary generalized tonic-clonic seizures in patients ≥ 13 years of age
4/25/2011				X	Monotherapy for partial seizures in patients ≥ 13 years of age
5/18/2015	X	X	X		Maintenance treatment of bipolar disorder in patients ≥13 years of age was not established safe and effective
* IR = immediate release, CD = chewable dispersible, ODT = orally disintegrating tablet, XR = extended release					

8.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatics structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.3 APPENDIX C. DRUG UTILIZATION DATABASE DESCRIPTIONS

IQVIA, National Sales Perspectives™, Retail and Non-Retail

IQVIA, National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of eaches and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings. Based on IQVIA National Sales Perspectives™ database, the majority or 83% of all lamotrigine bottles of tablets were distributed to U.S. outpatient retail pharmacy settings in 2017. As a result, our analysis was focused on the outpatient retail pharmacy setting only and cannot be applied to other settings where these products are used such as hospitals.

IQVIA, Total Patient Tracker™ (TPT)

IQVIA, Total Patient Tracker™ (TPT) is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the National Prescription Audit (NPA) database which measures the "retail outflow" of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. NPA receives over 3.5 billion prescription claims per year, captured from a sample of the universe of approximately 59,400 pharmacies throughout the U.S. Estimates provided in this review are national estimates, but statistical tests were not performed to determine whether statistically significant changes occurred over time or between products; therefore, all changes over time should be considered approximate. In addition, these results cannot be validated through medical chart reviews

8.4 APPENDIX D. FAERS LINE LISTING OF THE 9 PEDIATRIC CASES FOR DISCUSSION

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Serious Outcome(s)*
1	2018-03-01	14584906	1	US-ALKEM LABORATORIES LIMITED-US-ALKEM-2018-00853	EXPEDITED	1.00000	Female	HO, OT
2	2018-02-22	14560628	1	US-ALKEM LABORATORIES LIMITED-US-ALKEM-2018-00682	EXPEDITED	3.00000	Male	OT
3	2016-01-13	11913398	1	US-MALLINCKRODT-T201505958	EXPEDITED	8.00000	Male	DE
4	2018-02-22	14560626	1	US-ALKEM LABORATORIES LIMITED-US-ALKEM-2018-00674	EXPEDITED	10.00000	Female	OT
5	2018-02-22	14560635	1	US-ALKEM LABORATORIES LIMITED-US-ALKEM-2018-00683	EXPEDITED	11.00000	Male	OT
6	2015-12-28	11870341	1	US-TARO PHARMACEUTICALS USA.,INC-2015SUN02309	EXPEDITED	16.00000	Male	HO
7	2018-03-28	14690907	1	PHHY2018US047492	EXPEDITED	16.00000	Male	DE, OT
8	2017-01-06	13092260	1	US-JNJFOC-20161226211	EXPEDITED	16.00000	Female	DE, HO
9	2017-12-01	14241798	1	US-TORRENT-00004840	EXPEDITED	16.00000	Female	DE

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events. This outcome should not be confused with the clinical outcome of the reported adverse drug experience. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A report may have more than one serious outcome.
Abbreviations: DE=Death, HO=Hospitalization, LT= Life-threatening, DS= Disability, CA= Congenital Anomaly, OT=Other medically significant

8.5 APPENDIX E. THE HUNTER SEROTONIN TOXICITY CRITERIA

The presence of a serotonergic agent and any one of the following clinical findings:

- Spontaneous clonus
- Inducible clonus and agitation or diaphoresis
- Ocular clonus ("ping pong eyes") and agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and temperature > 38°C (100.4°F) and ocular clonus or inducible clonus

8.6 APPENDIX F. FAERS AND LITERATURE SEARCH STRATEGY

FAERS Search Strategy Lamotrigine and Serotonin Syndrome	
Date of Search	June 29, 2018
Time Period of Search	All reports through June 25, 2018
Search Type	Drug Safety Analytics Dashboard (DSAD) Quick Query
Product Terms	Product active ingredient: lamotrigine
MedDRA Search Terms (Version 20.1)	Serotonin syndrome (PT)
Search Parameters	All ages 17 years and older

FAERS Search Strategy Lamotrigine and Tubulointerstitial Nephritis	
Date of Search	June 25, 2018
Time Period of Search	All reports through June 25, 2018
Search Type	Drug Safety Analytics Dashboard (DSAD) Quick Query
Product Terms	Product active ingredient: lamotrigine
MedDRA Search Terms (Version 20.1)	Tubulointerstitial nephritis (PT)
Search Parameters	All ages 17 years and older

FAERS Search Strategy Lamotrigine and Oculogyric Crisis	
Date of Search	June 25, 2018
Time Period of Search	All reports through June 25, 2018
Search Type	Drug Safety Analytics Dashboard (DSAD) Quick Query
Product Terms	Product active ingredient: lamotrigine
MedDRA Search Terms (Version 20.1)	All PT terms
Search Parameters	All ages 17 years and older

Literature Search Strategy for Lamotrigine and Serotonin Syndrome	
Date of Search	July 11, 2018
Database	PubMed
Search Terms	("lamotrigine"[Supplementary Concept] OR "lamotrigine"[All Fields]) AND ("serotonin syndrome"[MeSH Terms] OR ("serotonin"[All Fields] AND "syndrome"[All Fields]) OR "serotonin syndrome"[All Fields])
Years Included in Search	All years
Limits	Human, case report, full text, English

Literature Search Strategy for Lamotrigine and Tubulointerstitial Nephritis	
Date of Search	July 11, 2018
Database	PubMed

Literature Search Strategy for Lamotrigine and Tubulointerstitial Nephritis	
Search Terms	("lamotrigine"[Supplementary Concept] OR "lamotrigine"[All Fields]) AND ("nephritis, interstitial"[MeSH Terms] OR ("nephritis"[All Fields] AND "interstitial"[All Fields]) OR "interstitial nephritis"[All Fields] OR ("tubulointerstitial"[All Fields] AND "nephritis"[All Fields]) OR "tubulointerstitial nephritis"[All Fields])
Years Included in Search	All years
Limits	Human, case report, full text, English

Literature Search Strategy for Lamotrigine and Oculogyric Crisis	
Date of Search	July 11, 2018
Database	PubMed
Search Terms	“lamotrigine oculogyric crisis”
Years Included in Search	All years
Limits	Human, case report, full text, English

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