

One Year Post-Exclusivity Adverse Event Review: Lamotrigine

**Pediatric Advisory Committee Meeting
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Background Drug Information

Drug: Lamictal® (lamotrigine)

Therapeutic Category: Antiepileptic drug (AED)

Sponsor: GlaxoSmithKline

Original Market Approval: December 27, 1994

Pediatric Exclusivity Granted: February 14, 2007

Current Indications

Epilepsy

- Adjunctive therapy for partial seizures, the generalized seizures of Lennox-Gastaut syndrome, and primary generalized tonic-clonic seizures in adults and **pediatric patients ≥ 2 years old**
- Conversion to monotherapy in adults with partial seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as a single AED

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Current Indications (continued)

Bipolar Disorder

- Maintenance treatment to delay the time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in adults treated for acute mood episodes with standard therapy

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Drug Use Trends in Outpatient Settings During the Post-Exclusivity Period

7.2 million dispensed prescriptions for all age groups

- 648,773 (9%) for patients 0 to 16 years old
- 1,149 (0.02%) for patients < 2 years old*

22% increase in prescriptions for all age groups
between the 12 month pre- and post-exclusivity
periods

- 12% increase for patients 0 to 16 years old
- 11% decrease for patients < 2 years old*

*Lamotrigine is not indicated for pediatric patients < 2 years old.
SDI Vector One®: National. Mar 2007 – Feb 2008. Data extracted 6-2008. 5

Drug Use Trends in Outpatient Settings During the Post-Exclusivity Period

Psychiatry was the top prescribing specialty†

- Psychiatrists - 50.4%
- Neurologists - 18.3%
- Pediatricians - 1.1%

Top diagnosis codes in patients 0 to 16 years old ‡

- Related to epilepsy - 51%
- Related to Bipolar Disorder - 34%

†SDI Vector One®: National. Mar 2007 – Feb 2008. Data extracted 6-2008.
‡SDI Physician's Drug and Diagnosis Audit. Mar 2007 – Feb 2008. Extracted 6-2008. 6

Selected Pediatric Labeling Prior to the Written Request for Exclusivity Studies

Boxed Warning

- Serious, life-threatening, and fatal rashes in adults and pediatric patients

Indications

- Adjunctive therapy for the generalized seizures of Lennox-Gastaut syndrome in adults and pediatric patients ≥ 2 years old

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Pediatric Exclusivity Studies: Overview

Proposed Use

- Adjunctive therapy for partial seizures in pediatric patients 1 month to 16 years old

Study Types

≥ 2 years old

- Efficacy, Short-term Safety, and Pharmacokinetic (PK) Study

1 to 24 months old

- Efficacy, Short-term Safety, and PK Study
- Longer-term Safety and PK Study

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Pediatric Exclusivity Studies: Findings

≥ 2 years old

- Study demonstrated efficacy for adjunctive treatment of partial seizures
- Serious rashes, including 1 rash-related death, were seen in pediatric patients receiving adjunctive therapy.

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Pediatric Exclusivity Studies: Findings

1 to 24 months old

- Unable to determine that lamotrigine is safe and effective for adjunctive treatment of partial seizures
 - Protocol-specified analyses failed to detect a statistically significant treatment difference between adjunctive lamotrigine versus adjunctive placebo therapy
 - Adverse event data needed reanalysis using coding schemes more appropriate for a population unable to communicate symptoms

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Pediatric Exclusivity Studies: Outcomes

≥ 2 years old

- Lamotrigine was approved for the studied use.
- Safety data were incorporated into the drug labeling.

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Pediatric Exclusivity Studies: Outcomes

1 to 24 months old

- Lamotrigine was not approved for the studied use.
- Action was prior to reauthorization of the Best Pharmaceuticals for Children Act (BPCA) 2007.
- No labeling change was made as labeling of negative pediatric studies was not required when these studies were reviewed.
- The Division of Neurology Products acknowledges that labeling the study data for 1 to 24 month olds would be consistent with BPCA 2007

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Pediatric Exclusivity Studies: Summary of Labeling Changes

Labeling Sections Changed

- Boxed Warning
- Clinical Pharmacology
- Clinical Studies
- Indications and Usage
- Warnings
- Precautions
- Adverse Reactions

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Pediatric Exclusivity Studies: Details of Safety Labeling Changes

Boxed Warning

Updated the pediatric serious rash data

- Incidence of serious rash in pediatric patients receiving adjunctive therapy was 0.8%.
 - Incidence reported to be 1% in the previous labeling.
- One rash-related death was reported out of 1,983 pediatric patients on adjunctive therapy.

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Pediatric Exclusivity Studies: Details of Safety Labeling Changes

Clinical Pharmacology, Age: Pediatric Patients

- Lamotrigine clearance was influenced predominantly by total body weight and concurrent AED therapy.
 - Not significantly influenced by age
- Oral clearance was higher, on a body weight basis, in pediatric patients < 30 kg than in adults.
- Patients weighing < 30 kg may need an increase of as much as 50% in maintenance doses, based on clinical response.

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Pediatric Exclusivity Studies: Details of Safety Labeling Changes

Warnings, Serious Rash: Pediatric Population

- Incidence of serious rash in pediatric patients receiving adjunctive therapy was 0.8% (16 of 1,983).
- One rash-related death was reported in the 1,983 pediatric patient cohort.
- Concomitant valproic acid (VPA) use increases the risk of potentially life-threatening rash.
 - 1.2% (6 of 482) with concomitant VPA use
 - 0.6% (6 of 952) without concomitant VPA use

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Pediatric Exclusivity Studies: Details of Safety Labeling Changes

Warnings, Acute Multiorgan Failure

- Fatalities associated with multiorgan failure and various degrees of hepatic failure were reported in 4 of 2,435 pediatric patients.
- Majority of these deaths occurred in association with other serious medical events, including status epilepticus, overwhelming sepsis, and hantavirus. ¹⁷

Pediatric Exclusivity Studies: Details of Safety Labeling Changes

Adverse Reactions: Adjunctive Therapy in Pediatric Patients

- ***Most common adverse events*** (AEs) (> 5%): Infection, vomiting, rash, fever, somnolence, accidental injury, dizziness, diarrhea, abdominal pain, nausea, ataxia, tremor, asthenia, bronchitis, flu syndrome, and diplopia

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Pediatric Exclusivity Studies: Details of Safety Labeling Changes

Adverse Reactions: Adjunctive Therapy in Pediatric Patients

Discontinuations due to AEs

- 339 pediatric patients with partial seizures or Lennox-Gastaut
 - 4.2% (lamotrigine group) and 2.9% (placebo group)
 - Most commonly reported AEs: rash (lamotrigine group) and deterioration of seizure control (placebo group)

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Pediatric Exclusivity Studies: Details of Safety Labeling Changes

Adverse Reactions: Adjunctive Therapy in Pediatric Patients

Discontinuations due to AEs (continued)

- 1,081 pediatric patients receiving lamotrigine in premarketing clinical trials
 - 11.5% discontinued due to an AE
 - Most commonly reported AEs: rash (4.4%), reaction aggravated (1.7%), and ataxia (0.6%)

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Pediatric Exclusivity Studies: Details of Safety Labeling Changes

Adverse Reactions, Incidence in Controlled Adjunctive Trials in Pediatric Patients

- Updated table of treatment-emergent adverse events in placebo-controlled, adjunctive trials

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Adverse Event Reports Since Marketing Approval

12/27/1994 – 06/23/2008

Crude Counts*	All Reports (US)	Serious** (US)	Death (US)
Adults (≥ 17)	8,100 (5,957)	5,055 (3,069)	572 (307)
Pediatrics (0 to 16)	1,787 (1,193) [12.5% of all reports]	1,250 (639)	106 (30)
Age unknown	4,368	1,905	161
All ages	14,255	8,210	839

* May include duplicate cases

** Serious adverse events include death, hospitalization, life-threatening event, disability, congenital anomaly, and other (unspecified).

Source: Adverse Event Reporting System, FDA

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Pediatric Deaths Since Marketing Approval

106 Crude count reports

- 23 Duplicates

83 Unique pediatric cases

- 38 Expected epilepsy complications
- 16 Labeled warnings and precautions
- 19 Adverse events with a high background rate in the general population (but lamotrigine cannot be excluded as a contributing factor)
- 10 Others

No new safety concerns were identified.

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Source: Adverse Event Reporting System, FDA

Labeling Relevant to the Death Cases

Boxed Warning

- Serious rashes in pediatric patients

Warnings

- Serious Rash: Pediatric Population

Precautions

- Sudden Unexplained Death in Epilepsy
- Status Epilepticus

Adverse Reactions

- Infection (Controlled Trials in Pediatric Patients with Epilepsy)
- Pancreatitis (Postmarketing and Other Experience)

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Pediatric Deaths Since Marketing Approval

38 Expected Epilepsy Complications

- 19 Seizure/prolonged seizure/status epilepticus
- 19 Found dead/death/sudden death

16 Labeled Warnings and Precautions

- 16 Rash/Stevens Johnson syndrome/
toxic epidermal necrolysis

Unlabeled serious adverse events (SAEs) are underlined.
Source: Adverse Event Reporting System, FDA

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Pediatric Deaths Since Marketing Approval

19 Adverse Events With a High Background Rate in the General Population

(but lamotrigine cannot be excluded as a contributing factor)

- 9 In utero exposures
 - Prematurity, congenital anomalies, complications of birth, or therapeutic abortion of fetus with neural tube defects
- 4 Pulmonary events
 - Pneumonia*/pulmonary infection*/aspiration pneumonopathy
- 1 case of each of the following
 - Sepsis*, Varicella infection*, MELAS syndrome progression, Genetic leukodystrophy, Fall and fractured skull/neck, Hit by truck

* Infection in broad terms is listed as an adverse reaction. Unlabeled SAEs are underlined.
Source: Adverse Event Reporting System, FDA

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Pediatric Deaths Since Marketing Approval

10 Other Death Cases

An association with lamotrigine is unclear because the cases include concomitant medications, underlying medical conditions, and/or insufficient details.

Source: Adverse Event Reporting System, FDA.

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Pediatric Deaths Since Marketing Approval

Cardiac Cases

- 10 year old male on lamotrigine monotherapy for 4 ½ years was found unconscious and could not be revived. Autopsy showed signs of myocarditis.
- 13 year old male experienced increasing seizures over 3 years of lamotrigine treatment. Topiramate was added. Two months later, he was admitted to the hospital for an unspecified reason, and he died suddenly. Autopsy found acute myocarditis.

Source: Adverse Event Reporting System, FDA

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Unlabeled SAEs are underlined.

Pediatric Deaths Since Marketing Approval

Cardiac Cases (continued)

- 16 year old experienced cardiac arrest 1 month after initiating lamotrigine and oxcarbazepine for unknown indications. He was hospitalized and died one week later.
 - Other concomitant drugs (diazepam and clobazam).
- 8 year old female was found dead 6 months after initiating lamotrigine to treat epilepsy. Autopsy found cardiac insufficiency and generalized inflammation of the respiratory tract.

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Source: Adverse Event Reporting System, FDA

Unlabeled SAEs are underlined.

Pediatric Deaths Since Marketing Approval

Pulmonary Cases

- 3 year old male with encephalopathy and oxygen treatment developed respiratory and cardiac failure after 18 months of lamotrigine therapy.
 - Concomitant drugs (valproic acid and trichloroacetaldehyde).
- 4 year old male, with global developmental delay and on lamotrigine for 1½ months to treat seizures, experienced fever and vomiting, a 30-minute seizure, and respiratory arrest and died.
 - Concomitant drugs (valproic acid, phenytoin, and melatonin)

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Source: Adverse Event Reporting System, FDA

Unlabeled SAEs are underlined.

Pediatric Deaths Since Marketing Approval

Hepatic

- 1 year old male developed unspecified cerebrovascular disorder, hepatic abnormality, and purpura after 1 year valproate sodium and 2 weeks lamotrigine treatment for epilepsy. He was hospitalized and died a few weeks later.
- 15 year old female experienced rash and discontinued lamotrigine after 3 weeks treatment for blackouts. The rash resolved, blackouts continued, occasional vomiting developed, and phenobarbital was started. Two days later (2½ weeks after lamotrigine was stopped), she was diagnosed with liver failure. A few days later, brain edema and death occurred. Reye's syndrome was considered.

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Source: Adverse Event Reporting System, FDA

Unlabeled SAEs are underlined.

Pediatric Deaths Since Marketing Approval

Other Cases

- 8 year old female on 2 years of lamotrigine and 2 months of topiramate therapy developed hemorrhagic pancreatitis and died within 20 hours.
- 10 year old male with multiple disabilities and on lamotrigine for 10 months developed renal failure and died. Amphotericin and acyclovir, both associated with renal failure, were started 2 days before the onset of the adverse event.

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Source: Adverse Event Reporting System, FDA

Unlabeled SAEs are underlined.

Adverse Event Reports Since Marketing Approval

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Source: Adverse Event Reporting System, FDA

Adverse Event Reports During the Post-Exclusivity Period

02/14/2007 – 03/14/2008

Crude Counts*	All Reports (US)	Serious** (US)	Death (US)
Adults (≥ 17)	1,898 (1,550)	1,060 (713)	159 (136)
Pediatrics (0 to 16)	303 (234)	172 (105)	2 (2)
Age unknown	1,105	431	18
All ages	3,306	1,663	179

* May include duplicate cases

** Serious adverse events include death, hospitalization, life-threatening event, disability, congenital anomaly, and other (unspecified).

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Source: Adverse Event Reporting System, FDA

Serious Adverse Events During the Post-Exclusivity Period

172 Crude count reports

398 Serious adverse events identified in ≥ 3 reports

(may include duplicates)

- 285 Labeled events
- 57 Unlabeled events
- 56 Events inappropriate for labeling because they can occur with all drugs (e.g., drug ineffective)

No new safety concerns were identified.

Source: Adverse Event Reporting System, FDA

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Labeling Relevant to the Serious Adverse Events

Boxed Warning

- *Serious rashes*, including toxic epidermal necrolysis

Warnings

- *Serious rash*: Stevens-Johnson syndrome, angioedema, fever, lymphadenopathy
- *Hypersensitivity reactions*: hypersensitivity, disseminated intravascular coagulation, lymphadenopathy
- *Multiorgan failure*: hepatic failure, disseminated intravascular coagulation, elevated transaminases
- *Blood dyscrasias*: thrombocytopenia

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Labeling Relevant to the Serious Adverse Events Adverse Reactions

Vomiting	Increased alanine or aspartate aminotransferase	Confusion	Visual disturbance
Fever	Epistaxis	CNS depression	Decreased weight
Irritability	Increased hepatic enzyme	Disseminated intravascular coagulation	Increased weight
Diarrhea	Hypotonia	Dyskinesia	
Headache	Insomnia	Dyspnea	
Malaise	Personality disorder	Hallucination	
Maculopapular rash	Kidney failure	Decreased memory	
Somnolence	Infection	Nausea	
Tremor	Anorexia	Pain	
Agitation	Bilirubinemia	Speech Disorder	37

Unlabeled Serious Adverse Events During the Post-Exclusivity Period (n= 57)

Crude Counts for Each Preferred Term	Preferred Term
8	Abnormal behavior
6	Aggression
4	Blister, Candidiasis, Coagulopathy, Septic shock
3	Abnormal feces, Anuria, Blood pressure decreased, Coordination abnormal, Dysmorphism, Hypotension, Jaundice, Lactose intolerance, Mucosal inflammation

No safety signal was identified.

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Source: Adverse Event Reporting System, FDA

Risk Management Activities: Suicidality and Antiepileptic Drugs

January 31, 2008 FDA Alert

- Patients on antiepileptic drugs (AEDs) should be closely monitored for behavior indicating suicidal thoughts or behavior or depression.
- FDA analyzed reports of suicidal behavior or ideation from placebo-controlled clinical studies of 11 AEDs.
 - 0.43% for patients on AEDs vs. 0.22% for patients on placebo
 - Results were generally consistent among the 11 drugs

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Risk Management Activities: Suicidality and Antiepileptic Drugs

January 31, 2008 FDA Alert (continued)

- AEDs included in the analyses:
carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproate, zonisamide
- FDA is working to include information on the risk of suicidality in the labelings of all antiepileptic drugs used for maintenance therapy.

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**Risk Management Activities:
Medication Errors Related to Name Confusion**

- Lamictal® is confused primarily with Lamisil®.
- Name confusion impacts both adult and pediatric populations.
- Reported medication errors in pediatric patients have not increased since pediatric exclusivity was granted.

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**Risk Management Activities:
Medication Errors Related to Name Confusion**

Interventions implemented to minimize name confusion

- Institute for Safe Medication Practices' (ISMP) Confused Drug Names List
- Extensive educational campaign
- Rx Safety Advisor pharmacy software program

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Risk Management Activities: Medication Errors Related to Name Confusion

FDA will continue to monitor for medication errors

- Assessing the communication programs developed by the Lamictal® Sponsor
- Monitoring the effectiveness of RX Safety Advisory
- Monitoring for name confusion

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Summary: Lamotrigine

- This completes the one year post-exclusivity adverse event reporting.
- At present, lamotrigine is not approved for use in patients under 2 years of age.
- Safety data from the pediatric exclusivity trial for 2 to 16 year olds have been incorporated into the drug labeling. The Division is planning to include information on the 1 to 24 month olds in labeling.
- The safety review did not reveal any new safety concerns for lamotrigine.

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Summary: Lamotrigine (continued)

- FDA is working to include suicidality data in the labeling of 11 antiepileptic drugs, including lamotrigine.
- FDA will continue to monitor medication errors related to Lamictal® name confusion.
- FDA will continue its standard, ongoing safety monitoring for lamotrigine.
- Does the Advisory Committee concur with this approach?

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