Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	October 18, 2010
To:	Lisa L. Mathis MD, Associate Director Pediatric and Maternal Health Staff (PMHS) Office of New Drugs (OND), CDER and M. Dianne Murphy, MD, Director Office of Pediatric Therapeutics (OPT), OC
Thru:	Cindy Kortepeter, PharmD, Team Leader Ann W. McMahon, MD, MS, Deputy Director Division of Pharmacovigilance I (DPV I) Office of Surveillance and Epidemiology (OSE), CDER
From:	Kelley M. Simms, PharmD, BCPS
Subject:	PREA: Pediatric Postmarketing Adverse Event
Drug Name(s):	Lamictal XR tablets
Pediatric Labeling Date:	May 29, 2009
Application Type/Number:	22115, 22509
Applicant/sponsor:	GlaxoSmithKline LLC
OSE RCM #:	2010-1232

CONTENTS

EXECUTIVE SUMMARY

In accordance with the Pediatric Research Equity Act (PREA), this review describes post-marketing adverse event reports in the Adverse Event Reporting System (AERS) database associated with Lamictal extended release (XR) tablets (Lamictal XR, GlaxoSmithKline LLC) that were reported in children 0-16 years old. The purpose of this review is to provide the Pediatric Advisory Committee (PAC) with post-marketing safety data so that they can advise the FDA regarding potential safety concerns in children associated with Lamictal XR tablets. In addition to pediatric reports for Lamictal XR, the Office of Pediatric Therapeutics (OPT) and the Pediatric and Maternal Health Staff (PMHS) requested a review of the most frequently reported adverse event terms for serious reports in AERS for Lamictal chewable dispersible (CD) tablets and Lamictal orally disintegrating tablets (ODT) in pediatric patients age 0-16 years.

Lamictal XR tablets were approved on May 29, 2009 as adjunctive therapy for partial onset seizures with or without secondary generalization in patients 13-years old and greater and on January 29, 2010 as adjunctive therapy for primary generalized tonic-clonic seizures.

The Adverse Event Reporting System (AERS) database was searched for all reports of adverse events (serious and non-serious) up to the "data lock" date of June 30, 2010. AERS contained 98 reports for Lamictal XR. Pediatric reports represent approximately 5% of the total (5/98). A review of the post-marketing AERS cases did not reveal any new safety concerns associated with the use of Lamictal XR in children. There were no cases of hepatotoxicity or aseptic meningitis, and no cases resulted in a fatal outcome.

There was one case of neonatal cyanosis occurring in a 16-day-old breastfed infant whose mother was taking Lamictal CD during and after her pregnancy. Due to the findings of this report, we recommend the following:

- DPV search the AERS database for any additional reports of adverse events possibly associated with infants exposed to lamotrigine via breast milk. DPV has already received a consult request from the Division of Neurology Products (DNP) for this issue.
- DNP follow-up with consultations to the Pediatric and Maternal Health Staff (PMHS) and to GlaxoSmithKline to ascertain additional information on drug exposure via breast milk in order to determine whether changes to the USE IN SPECIFIC POPULATIONS/Nursing Mothers section of the label are warranted.
- DPV continue to monitor for adverse event reports possibly associated with infants exposed to lamotrigine via breast milk.

1 BACKGROUND

1.1 PRODUCT FORMULATIONS AND INDICATIONS

Lamictal is available in the following formulations: Lamictal tablet, Lamictal chewable dispersible (CD) tablet, Lamictal orally disintegrating (ODT) tablet and Lamictal extended release (XR) tablets.

Lamictal XR tablets received FDA approval on May 29, 2009 and are indicated for:

- adjunctive therapy for primary generalized tonic-clonic (PGTC) seizures and partial onset seizures with or without secondary generalization in patients ≥13 years

Lamictal tablets, Lamictal Chewable Dispersible (CD) tablets and Lamictal Orally Disintegrating (ODT) tablets were approved December 27, 1994, August 24, 1998 and May 8, 2009, respectively. Each product is indicated for**:**

- **Epilepsy—adjunctive therapy in patients ≥2 years of age:**
  - partial seizures.
  - primary generalized tonic-clonic seizures.
  - generalized seizures of Lennox-Gastaut syndrome.
- **Epilepsy—monotherapy in patients ≥16 years of age:** conversion to monotherapy in patients with partial seizures who are receiving treatment with carbamazepine, phenobarbital, phenytoin, primidone, or valproate as the single AED.
- **Bipolar Disorder in patients ≥18 years of age:** maintenance treatment of Bipolar I Disorder to delay the time to occurrence of mood episodes in patients treated for acute mood episodes with standard therapy.

1.2 PEDIATRIC LABELING

The current pediatric indications for Lamictal XR tablets are for adjunctive therapy for primary generalized tonic-clonic (PGTC) seizures and partial onset seizures with or without secondary generalization in patients ≥13 years of age.[1] Of note, Lamictal XR has different indications and is approved for different ages than all other lamotrigine products. Relevant pediatric safety information from the current product label is shown in Appendix A.

Table 1. Approval History for Lamictal XR tablets

Approval Date	Summary of changes
May 29, 2009	Lamictal XR (25mg, 50mg, 100mg, 200mg) tablets approved as adjunctive therapy for partial onset seizures with or without secondary generalization in patients ≥13 years of age
January 29, 2010	Lamictal XR tablets approved as adjunctive therapy for primary generalized tonic-clonic (PGTC) seizures in patients ≥13 years of age.
April 14, 2010	Lamictal XR 300mg tablets were approved

2 METHODS AND MATERIALS

All pediatric reports in AERS for Lamictal XR, including a specific assessment of pediatric deaths, life-threatening rashes, hepatotoxicity, aseptic meningitis and serious unlabeled events, were evaluated. The timeframe consists of a data lock date from May 29, 2009 (the approval date for Lamictal XR) through June 2010.

The main focus of this review is to assess post-marketing reports of Lamictal XR for pediatric patients (0-16 years old) in accordance with PREA. In addition,, the AERS database was searched to determine crude counts of reports for all age groups, as well as the number of serious adverse events in adults compared to the pediatric population. Furthermore, serious, pediatric reports for other formulations (Lamictal CD and Lamictal ODT) were evaluated.

2.1 AERS SEARCH CRITERIA

We searched the AERS database on August 18, 2010 for all adverse event reports associated with Lamictal XR tablets using the following criteria:

- **Product(s):** Lamictal XR (Trade Name search)
- **NDA's:** 22115 & 22509
- **MedDRA adverse event search terms:** all adverse events
- **FDA Received Date:** from market approval (May 29, 2009) to the data lock date of June 30, 2010
- **Age range:** all ages & zero to 16 years
- **Outcomes:** All & Serious

The AERS database was searched on August 25, 2010 using the following criteria:

- **Product(s):** Lamictal CD (Trade Name search)
- **NDAs:** 20764
- **ANDAs:** 90401, 76701, 79099, 76630, 79204, 76420, 76928, 78009
- **MedDRA adverse event search terms:** all adverse events
- **FDA Received Date:** May 29, 2009 to the data lock date of June 30, 2010
- **Age range:** Zero to 16 years
- **Outcomes:** Serious

AND

- **Product(s):** Lamictal ODT (Trade Name search)
- **NDA:** 22251
- **MedDRA adverse event search terms:** all adverse events
- **FDA Received Date:** May 29, 2009 up to the data lock date of June 30, 2010
- **Age range:** Zero to 16 years
- **Outcomes:** Serious

2.2 PUBLISHED CASE REPORTS

We searched the medical literature (PubMed@FDA) on August 24, 2010 for case reports of adverse events associated with Lamictal XR tablets using the search string "Lamictal XR."

3 RESULTS

3.1 AERS RESULTS FOR LAMICTAL XR TABLETS

3.1.1 CRUDE COUNTS OF ALL AERS REPORTS FOR LAMICTAL XR TABLETS

Table 2: Crude counts[1] of AERS Reports from all sources for Lamictal XR from approval date of May 29, 2009 to the data lock date of June 30, 2010

	All reports (US)[2]	Serious[3] (US)	Death (US)
Adults (≥ 17 yrs.)	57 (57)	21 (21)	1 (1)
Pediatrics (0-16 yrs.)	5 (5)	3 (3)	0 (0)
Age unknown (Null values)	36 (36)	15 (15)	0 (0)
Total	98 (98)	39 (39)	1 (1)

[1] May include duplicates

[2] US counts in parentheses

[3] Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention to prevent permanent impairment/damage and other serious important medical events.

3.1.2 CASE CHARACTERISTICS FOR LAMICTAL XR

The AERS search retrieved five total Lamictal XR adverse event reports in children zero to 16 years old representing approximately 5% of the total (5/98). Appendix B contains a line listing of all five cases. There is a preponderance of females in the case series and age ranged from 7-16 years old. Three cases were reported as serious, and no deaths were reported.

Table 3 : Characteristics of AERS cases associated with the use of Lamictal XR tablets in pediatric patients (0-16 years old), received by the FDA from market approval to the data lock date of June 30, 2010 (n=5)

Gender [n=5]	Male: 1 Female: 4
Age [n=5]	0- <1 month: 0 1 month <2 yrs: 0 2-5 yrs: 0 6-11 yrs: 2 12-16 yrs: 3 Mean: 12.4 years Median: 14 years Range: 7-16 years
Origin [n=5]	US=5 Foreign=0
Event date (n=5)	2009: 2 2010: 3
Daily dose[1] [n=5]	Average=205mg , Median=100mg , Range=25-500mg
Duration of therapy[2] [n=5]	Average=48 days , Median=30 days Range=0-120 days
Reasons for use [n=5]	Seizure disorder
Serious Outcomes [n=3]	Hospitalization: 1 Other Medically Serious: 2

[1] Dosing recommendations for patients 13 years of age and up depend upon concomitant medications. Escalation begins as low as 25mg every other day and may increase over eight weeks up to 600mg/day (the highest recommended dose).

[2] Duration of therapy was given a value of zero if the adverse event occurred the same day as starting Lamictal XR. If exact dates were not provided, then the duration was estimated based on information provided.

3.2 AERS RESULTS FOR LAMICTAL XR, LAMICTAL ODT AND LAMICTAL CD TABLETS

3.2.1 CRUDE COUNTS OF ALL SERIOUS PEDIATRIC AERS REPORTS FOR LAMICTAL XR, LAMICTAL ODT AND LAMICTAL CD TABLETS

Table 4: Crude counts[1] of all AERS reports from all sources for pediatric patients (age 0-16 years) with *serious outcomes*[2] from May 29, 2009 to June 30, 2010

	Lamictal XR	Lamictal CD	Lamictal ODT
0 – 7 years old	0	20	6
8 – 12 years old	1	20	6
13 – 16 years old	2	18	4
Age unknown (Null values)	0	5	4
Total	3	63	20

[1] May include duplicates

[2] Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention to prevent permanent impairment/damage and other serious important medical events.

All labeled adverse events/MedDRA preferred terms reported for Lamictal XR and all labeled adverse events/MedDRA preferred terms reported in at least 2 serious reports for Lamictal CD and Lamictal ODT in children 0-16 years old, received by the FDA from May 29, 2009 to June 30, 2010 are shown below in Appendix C.

3.2.2 UNLABELED PEDIATRIC ADVERSE EVENTS FOR LAMICTAL XR, LAMICTAL ODT AND LAMICTAL CD TABLETS

There was one non-serious case of bruxism reported in a 15-year old-female taking Lamictal XR. At the time of report, the patient continued to take Lamictal XR and the event was unresolved. Table 5 below lists all unlabeled, serious MedDRA PTs with a count of two or greater for Lamictal CD. There were no unlabeled MedDRA PTs coded in at least two pediatric reports for Lamictal ODT tablets.

Table 5. Crude counts[1] of unlabeled, serious[2] adverse events reported for Lamictal CD tablets in children 0-16 years old, received by the FDA from May 29, 2009 to June 30, 2010[3]		
PT	**Count**	**Drug name**
Toxic Shock Syndrome[4]	4	"Lamictal CD tablets"
Autism	3	Lamictal CD tablets
Hypernatremia[4]	3	"Lamictal CD tablets"
Lactose intolerance	3	Lamictal CD tablets
Cyanosis neonatal[4]	2	"Lamictal CD tablets"

[1] May include duplicates

[2] Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention to prevent permanent impairment/damage and other serious important medical events.

[3] There were no unlabeled MedDRA PTs for Lamictal ODT tablets coded in at least two pediatric reports.

[4] Coded for Lamictal CD tablets, but actual dosage form of lamotrigine was not specified in the report.

A hands-on analysis was performed for all unlabeled, serious events listed in Table 5. After duplicate reports were reconciled, the unlabeled PTs shown in Table 5 above were captured in three unique cases. A summary of the three cases follow:

Toxic Shock Syndrome (n=1) and Hypernatremia (n=1)

This literature case describes an 11-year-old female who was prescribed sodium valproate for her seizures. The patient developed hair loss and was prescribed lamotrigine with the aim of discontinuing the sodium valproate after tapering. A lamotrigine-induced rash and fever were diagnosed on day 13. Lamotrigine was discontinued and the patient was admitted to the hospital. Over the next 36 hours, fevers continued to spike to 40°C, and she developed drowsiness and hypotension. She was transferred to the intensive care unit (ICU) and required intubation and ventilation. She exhibited a maculopapular blanching rash over her trunk, upper legs, and arms, with erosions over the hard palate and a hemorrhagic bulla on her lower lip, rhabdomyolysis, hypernatremia and multiorgan failure. She was treated for possible toxic shock syndrome, but blood cultures and viral studies were negative. She was provided supportive care and sodium valproate was discontinued. She was discharged after 19 days in the ICU, and was restarted on sodium valproate after a full recovery from organ failure.[2] [*Reviewer's notes:* the dermatologist in DPV reviewed this literature case and did not believe this patient exhibited a life-threatening rash of Stevens-Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN). However, the skin rash and other clinical findings satisfied the criteria for a severe case of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) or Drug Hypersensitivity Syndrome (DHS).]

Autism (n=1) and lactose intolerance (n=1)

A female, born in 1995, with a past medical history of fungal infections due to candida overgrowth and lactose intolerance is on a restricted anticandida diet and nutritional

supplements. The patient began experiencing seizures in 2005, and according to the neurologist, in January 2006 the patient was taking Lamictal CD 125mg/day and phenytoin (90mg/5mL) 340mg/day for seizures. The patient also has a diagnosis of autism spectrum disorder. The physician feels that this patient's medical "difficulties" are related to gut dysbacteriosis and did not indicate lamotrigine to be a causative agent.

Neonatal cyanosis (n=1)

A literature case describes a neonate's mother who was receiving lamotrigine 850mg/day at the time of report. The dosage was being slowly reduced by 25mg/week from the second week postpartum. A 16-day-old, fully-breastfed male experienced a brief episode of apnea that resolved when he was picked up. Three hours later he became cyanotic. After six minutes of continuous chest compressions he had normal skin color and regular, spontaneous respirations. There were no signs of infection and all blood tests were reportedly normal. His lamotrigine serum concentration was 4.87mcg/mL, and breastfeeding was discontinued at 17-days postpartum. The proposed pediatric therapeutic range is 1-5mcg/mL.[3] The neonate fully recovered from the event.[4]

3.3 LITERATURE SEARCH RESULTS

The literature search did not identify any additional case reports of adverse events associated with the use of Lamictal XR tablets.

4 DISCUSSION/SUMMARY OF PEDIATRIC CASES

The literature case in section 3.2.2 describing an 11-year old-female documented a rash. The dermatologist in DPV evaluated the case and found the skin rash and other clinical findings consistent with the criteria for DRESS or DHS. Hypersensitivity reactions are well-documented in the WARNINGS AND PRECAUTIONS section of the Lamictal XR label (see Appendix A - Warnings and Precautions: Hypersensitivity Reactions).

Another literature case in section 3.2.2 describing a 16-day-old, fully-breastfed male documented cyanosis. The current labeling is shown in Appendix A - Use in Special Populations: Nursing Mothers.

The literature case documents significant transfer from the mother to the neonate through breast milk. The mother experienced a seizure after delivery, and a more gradual dose reduction than originally planned was recommended. As the mother's clearance of lamotrigine decreased to preconception levels, her serum concentrations increased, and the neonate's serum lamotrigine concentration was found to be at the upper end of the proposed pediatric therapeutic range which is a possible explanation for the cyanotic episode.[4] Further explanation of this possibility is warranted and is discussed under "RECOMMENDATIONS" below.

The Lamictal XR label appropriately describes hypersensitivity reactions. There were no cases of hepatotoxicity or aseptic meningitis, and no cases resulted in death. Based on the

limited number of reports in this case series, we did not identify any new significant safety concerns associated with Lamictal XR in children 0-16 years old.

5 CONCLUSION

Lamictal oral tablets were approved December 1994. Subsequently, Lamictal CD was approved in August 1998, and Lamictal ODT and Lamictal XR were approved May 2009. Since the active moiety has been on the market for more than 15 years, and the adverse events are not expected to vary between formulations, most reported adverse events are adequately labeled. We are mindful of the fact that a limited number of reports do not necessarily mean the absence of a signal.

6 RECOMMENDATIONS

- DPV search the AERS database for any additional reports of adverse events possibly associated with infants exposed to lamotrigine via breast milk. DPV has already received a consult request from the Division of Neurology Products (DNP) for this issue.
- DNP follow-up with consultations to the Pediatric and Maternal Health Staff (PMHS) and to GlaxoSmithKline to ascertain additional information on drug exposure via breast milk in order to determine whether changes to the USE IN SPECIFIC POPULATIONS/Nursing Mothers section of the label are warranted.
- DPV continue to monitor for adverse event reports possibly associated with infants exposed to lamotrigine via breast milk.

7 REFERENCES

1. Lamictal XR (lamotrigine) Extended-Release Tablets Prescribing Information. GlaxoSmithKline. Research Triangle Park, NC. April 14, 2010.

2. Ferguson LP, Dargan PI, Hood JL, Tibby SM. Life-threatening organ failure after lamotrigine therapy. Pediatr Neurol. 2009;40:392-394.

3. Taketomo CK, Hodding JH, Kraus DM, eds. Pediatric dosage handbook. 15th ed. Hudson, OH: Lexi-Comp, 2008-2009:1011-7.

4. Nordmo E, et al. Severe apnea in an infant exposed to lamotrigine in breast milk. Ann Pharmacother. 2009 Nov;43(11):1893-7.

8 APPENDICES

Appendix A: Relevant pediatric safety information from the current product labeling.

Appendix B: Line listing of AERS cases associated with the use of Lamictal XR tablets in children 0-16 years old, received by the FDA from market approval to June 30, 2010. (n=5).

Appendix C: All labeled adverse events reported for Lamictal XR and crude counts[1] of labeled serious adverse events reported in at least 2 reports for Lamictal CD and Lamictal ODT in children 0-16 years old, received by the FDA from May 29, 2009 to June 30, 2010.

8.1 APPENDIX A. RELEVANT SAFETY INFORMATION FROM THE CURRENT PRODUCT LABELING.[1]

Black Box Warning: Serious Skin Rashes	LAMICTAL® XR™ can cause serious rashes requiring hospitalization and discontinuation of treatment. The incidence of these rashes, which have included Stevens-Johnson syndrome, is approximately 0.8% (8 per 1,000) in pediatric patients (2 to 16 years of age) receiving the immediate-release formulation of LAMICTAL as adjunctive therapy for epilepsy and 0.3% (3 per 1,000) in adults on adjunctive therapy for epilepsy. In a prospectively followed cohort of 1,983 pediatric patients (2 to 16 years of age) with epilepsy taking the adjunctive immediate-release formulation of LAMICTAL, there was 1 rash-related death. LAMICTAL XR is not approved for patients under the age of 13 years. In worldwide postmarketing experience, rare cases of toxic epidermal necrolysis and/or rash-related death have been reported in adult and pediatric patients, but their numbers are too few to permit a precise estimate of the rate.
Contraindications	LAMICTAL XR is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.
Warnings and Precautions: Serious Skin Rashes	Pediatric Population: The incidence of serious rash associated with hospitalization and discontinuation of the immediate-release formulation of LAMICTAL in a prospectively followed cohort of pediatric patients (2 to 16 years of age) with epilepsy receiving adjunctive therapy with immediate-release lamotrigine was approximately 0.8% (16 of 1,983). When 14 of these cases were reviewed by 3 expert dermatologists, there was considerable disagreement as to their proper classification. To illustrate, one dermatologist considered none of the cases to be Stevens-Johnson syndrome; another assigned 7 of the 14 to this diagnosis. There was 1 rash-related death in this 1,983-patient cohort. Additionally, there have been rare cases of toxic epidermal necrolysis with and without permanent sequelae and/or death in US and foreign postmarketing experience. There is evidence that the inclusion of valproate in a multidrug regimen increases the risk of serious, potentially life-threatening rash in pediatric patients. In pediatric patients who used valproate concomitantly, 1.2% (6 of 482) experienced a serious rash compared with 0.6% (6 of 952) patients not taking valproate. LAMICTAL XR is not approved in patients under the age of 13 years.
Warnings and Precautions: Hypersensitivity Reactions	Hypersensitivity reactions, some fatal or life-threatening, have also occurred. Some of these reactions have included clinical features of multiorgan failure/dysfunction, including hepatic abnormalities and evidence of disseminated intravascular coagulation. 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 XR should be discontinued if an alternative etiology for the signs or symptoms cannot be established. **Prior to initiation of treatment with LAMICTAL XR, 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 physician immediately.
Warnings and Precautions: Acute Multiorgan Failure	Multiorgan failure, which in some cases has been fatal or irreversible, has been observed in patients receiving the immediate-release formulation of LAMICTAL. Fatalities associated with 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 the immediate-release formulation of LAMICTAL in epilepsy clinical trials. Rare fatalities from multiorgan failure have been reported in compassionate plea and postmarketing use. The majority of these deaths occurred in association with other serious medical events, including status epilepticus and overwhelming sepsis, and hantavirus, making it difficult to identify the initial cause. Additionally, 3 patients (a 45-year-old woman, a 3.5-year-old boy, and an 11-year-old girl) developed multiorgan dysfunction and disseminated intravascular coagulation 9 to 14 days after the immediate-release formulation of LAMICTAL was added to their AED regimens. Rash and elevated transaminases were also present in all patients and rhabdomyolysis was noted in 2 patients. Both pediatric patients were receiving concomitant therapy with valproate, while the adult patient was being treated with carbamazepine and clonazepam. All patients subsequently recovered with supportive care after treatment with the immediate-release formulation of LAMICTAL was discontinued.
Warnings and Precautions: Blood Dyscrasias	There have been reports of blood dyscrasias with the immediate-release formulation of LAMICTAL that may or may not be associated with the hypersensitivity syndrome. These have included neutropenia, leukopenia, anemia, thrombocytopenia, pancytopenia, and, rarely, aplastic anemia and pure red cell aplasia.
Adverse Reactions: Postmarketing Experience with the Immediate-Release Formulation of Lamictal	Blood and Lymphatic: Agranulocytosis, hemolytic anemia, lymphadenopathy not associated with hypersensitivity disorder. Musculoskeletal: Rhabdomyolysis has been observed in patients experiencing hypersensitivity reactions.
Use in Special Populations: Nursing Mothers	Preliminary data indicate that lamotrigine passes into human milk. Because the effects on the infant exposed to lamotrigine by this route are unknown, breastfeeding while taking LAMICTAL XR is not recommended.
Use in Special Populations: Pediatric Use	LAMICTAL XR is indicated as adjunctive therapy for PGTC and partial onset seizures with or without secondary generalization in patients ≥13 years of age. Safety and effectiveness of LAMICTAL XR for any use in patients below the age of 13 have not been established. The immediate-release formulation of LAMICTAL is indicated for

	adjunctive therapy in patients ≥2 years of age for partial seizures, the generalized seizures of Lennox-Gastaut syndrome, and primary generalized tonic-clonic seizures. Safety and efficacy of the immediate-release formulation of LAMICTAL, used as adjunctive treatment for partial seizures, were not demonstrated in a small randomized, double-blind, placebo-controlled, withdrawal study in very young pediatric patients (1 to 24 months). The immediate-release formulation of LAMICTAL was associated with an increased risk for infectious adverse reactions (LAMICTAL 37%, Placebo 5%), and respiratory adverse reactions (LAMICTAL 26%, Placebo 5%). Infectious adverse reactions included bronchiolitis, bronchitis, ear infection, eye infection, otitis externa, pharyngitis, urinary tract infection, and viral infection. Respiratory adverse reactions included nasal congestion, cough, and apnea.
Clinical Pharmacology	When lamotrigine was administered to healthy volunteers (n = 18) receiving valproate, the trough steady-state valproate plasma concentrations decreased by an average of 25% over a 3-week period, and then stabilized. However, adding lamotrigine to the existing therapy did not cause a change in valproate plasma concentrations in either adult or pediatric patients in controlled clinical trials.
Clinical Pharmacology	Safety and effectiveness of LAMICTAL XR for use in patients below the age of 13 have not been established.
Patient Counseling Information	Prior to initiation of treatment with LAMICTAL XR, 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 physician immediately. Patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy. Patients should be advised to notify their physicians if they intend to breastfeed or are breastfeeding an infant.

8.2 APPENDIX B: LINE LISTING OF AERS CASES ASSOCIATED WITH THE USE OF LAMICTAL XR TABLETS IN CHILDREN 0-16 YEARS OLD, RECEIVED BY THE FDA FROM MARKET APPROVAL TO JUNE 30, 2010 (N=5)*

ISR #	Report type	Age (years)/ Sex	Serious outcome	Event year	Daily dose (mg)	Duration of tx	Concomitant medications	All Adverse Reactions coded (PTs)	Notes
6460973	Expedited (15-Day)	10 / M	HO	2009	25	0 days	Depakote	DRUG ADMINISTRATION ERROR, PYREXIA, RASH, VIRAL INFECTION	This case described a 10-year-old male patient who began taking Lamictal XR on 30 September 2009 for an unknown indication. Co-suspect medication included Depakote. His mother inadvertently gave him 25 mg daily instead of every other day as was prescribed and on 30 September 2009, the patient experienced rash and fever. The patient's family physician initially thought the symptoms were viral in nature, and therefore Lamictal was not stopped for four to five days after the onset of symptoms. Depakote was also discontinued on an unknown date, and neither product was restarted. At the time of reporting the events were resolved, and the physician felt the events were probably related to treatment with Lamictal. She also stated the events could have been associated with the erroneous administration of Lamictal daily instead of every other day.

ISR #	Report type	Age (years)/ Sex	Serious outcome	Event year	Daily dose (mg)	Duration of tx	Concomitant medications	All Adverse Reactions coded (PTs)	Notes
6542198	Expedited (15-Day)	16 / F	OT	2010	500	NR	Zonisamide	CONVULSION	This case described the occurrence of a breakthrough seizure in a 16-year-old female patient who received Lamictal XR for epilepsy. Co-suspect medication included Zonegran. In October 2008, the patient started lamotrigine at 500 mg daily. In January 2010, the physician decreased the Zonegran in order to transition to Lamictal XR monotherapy. On 11 January 2010, the patient experienced a breakthrough seizure. The dose of lamotrigine was increased and at the time of reporting the event was resolved.

ISR #	Report type	Age (years)/ Sex	Serious outcome	Event year	Daily dose (mg)	Duration of tx	Concomitant medications	All Adverse Reactions coded (PTs)	Notes
6630221	Expedited (15-Day)	14 / F	OT	2010	100	0 days	Levetiracetam	CONVULSION, FATIGUE	This case was reported by a consumer's mother and described the occurrence of seizures in a 14-year-old female patient who received Lamictal XR for partial seizures. The patient's past medical history included gastroesophageal reflux. Concurrent medication included Keppra. On 17 February 2010, the patient started lamotrigine at 100 mg daily. On 17 February 2010, the mother of the patient reported that her daughter experienced seizure and exhaustion. The report also states when her daughter's dose increased from 50 mg to 100 mg, the patient experienced exhaustion. Finally, she reported that her daughter started the Lamictal XR green starter kit on 17 February 2010, and had seizure activity on 17 February 2010 and 19 February 2010. [*Reviewer's notes:* The "Green XR Kit" contains tablets beginning at 50mg. The mother stated that the patient started lamotrigine 100mg, and not 50mg on 17 February 2010. However, later the mother reports her daughter experienced exhaustion when her dose increased from 50mg to 100mg. This report contains conflicting information.]
6801281	Periodic	7 / F	NR	2009	100	30 days	NR	MYOPIA, VISION BLURRED	This case was reported by a consumer and described the occurrence of nearsightedness worsening in a 7-year-old female patient who received Lamictal XR for seizures. In August 2009, the patient started lamotrigine at 50 mg twice per day. Approximately 1 month later, in September 2009, the patient experienced nearsightedness worsening and blurred vision. Treatment with lamotrigine was continued. At the time of reporting, the outcome of the events were unknown.

ISR #	Report type	Age (years)/ Sex	Serious outcome	Event year	Daily dose (mg)	Duration of tx	Concomitant medications	All Adverse Reactions coded (PTs)	Notes
6801283	Periodic	15 / F	NR	2010	300	4 months	Folic acid, Clonazepam	BRUXISM	In September 2009, the 15-year-old female patient started Lamictal XR at 300 mg daily for epilepsy. On January 2010, the patient experienced bruxism (teeth grinding). Concurrent medications included folic acid and clonazepam. Treatment with lamotrigine was continued. At the time of reporting, the event was unresolved. The physician reported the patient takes Lamictal XR one 100 mg tablet in the morning and two 100 mg tablets in the evening.

* HO = hospitalization – initial or prolonged; OT = Other serious (important medical events); NR = None reported

8.3 APPENDIX C: ALL LABELED ADVERSE EVENTS REPORTED FOR LAMICTAL XR AND CRUDE COUNTS[1] OF LABELED ADVERSE EVENTS REPORTED IN AT LEAST 2 SERIOUS REPORTS FOR LAMICTAL CD AND LAMICTAL ODT IN CHILDREN 0-16 YEARS OLD, RECEIVED BY THE FDA FROM MAY 29, 2009 TO JUNE 30, 2010.[2]

	Count of reports by Lamictal formulation				
PT	XR	CD	ODT	Label Status	Other term(s) used in label
Convulsion	2	13	2	IR, DR, W/P, AR, OD, PCI, MG	Seizure
Aggression		10		W/P, PCI, MG	Aggressive, changes in mood
Psychomotor hyperactivity		9		MG	Restless
Drug ineffective		8		UI	
Pyrexia	1	7	4	W/P, AR, PCI, MG	Fever
Rash	1	7	2	BW, W/P, AR, PCI, MG	
Irritability		6		AR, MG	
Drug interaction		5	2	W/P, DI	Pharmacokinetic interactions
Rhabdomyolysis		5		W/P, AR	
Stevens-Johnson syndrome		5		BW, W/P, AR	
Blister		4		AR	Vesiculobullous rash
Crying		4		AR	Dysphoria
Disseminated Intravascular Coagulation		4		W/P	
Drug eruption		4		BW, W/P, AR, PCI, MG	Rash
Drug exposure during pregnancy		4		USP, PCI, MG	
Hypotension		4		AR	
Mucosal erosion		4		AR	Mouth ulceration, Stomach ulcer
Renal failure		4		W/P, AR, PCI	Multiorgan failure, acute kidney failure
Skin exfoliation		4		AR	Exfoliative dermatitis
Somnolence		4		AR, DI, PCI	
Toxic epidermal necrolysis		4	2	BW, W/P	
Abnormal faeces		3		AR	Diarrhea
Candidiasis		3		AR, USP, MG	Infection
Depressed level of consciousness		3		OD	

Diarrhoea		3		AR	
Drug dispensing error		3	2	UI	
Drug exposure via breast milk		3		USP, PCI, MG	Breastfeeding
Epistaxis		3		AR	
Gastrointestinal hemorrhage		3		AR	Rectal hemorrhage
Headache			3	AR, MG	
Insomnia		3		AR, MG	
Lymphadenopathy		3	5	W/P, AR, PCI	
Malaise		3		AR, MG	Fatigue
Periorbital Oedema		3		AR	Facial edema, edema
Rash papular		3	2	BW, W/P, AR, PCI, MG	Rash
Social avoidant behaviour		3		W/P, PCI, MG	Unusual changes in mood or behavior
Upper limb fracture		3		AR	Pathological fracture
Upper respiratory tract infection		3		AR, USP, MG	Infection
Vaginal hemorrhage		3		AR	Hemorrhage
Vomiting projectile		3		AR, MG	Vomiting
Abnormal behaviour		2		W/P, PCI, MG	Unusual changes in mood or behavior
Anxiety		2		AR, MG	
Aphasia		2		AR	
Coma		2		OD	
Completed suicide			2	W/P, AR, PCI, MG	
Condition aggravated		2		UI	
Disturbance in attention		2		AR	Concentration disturbance
Drug hypersensitivity		2		W/P, C, AR, PCI,	
Drug toxicity		2		W/P, USP	Toxicity
Drug withdrawal syndrome neonatal		2		W/P, AR, USP	Withdrawal
Epilepsy			2	DR, IR	
Eye disorder		2		W/P, AR, MG	Binding in the eye, dry eyes, eye infection, painful sores around your eyes
Grand Mal Convulsion		2		IR, DR, W/P, AR, OD, PCI, MG	Seizure
Hallucination		2		AR	
International Normalized Ratio Increased		2		MG	Unusual bleeding
Maternal drugs affecting foetus		2		UI ,USP, PCI, MG	Pregnancy, pregnant
Multi-organ failure		2		W/P, AR, PCI	
Oropharyngeal pain		2	2	AR	Pain

Pain		2		AR	
Petechiae		2		AR	
Pharyngeal oedema		2		W/P, AR, MG	Angioedema, edema, tongue edema, swelling of lips or tongue
Pneumonia		2		AR, USP, MG	Infection, infectious adverse reactions
Rash generalized		2		BW, W/P, AR, PCI, MG	Rash
Rash maculo-papular				BW, W/P, AR, PCI, MG	Rash
Skin discolouration		2		AR	
Thrombocytopenia			2	W/P, AR	
Tremor		2		AR, MG	
Urinary retention		2		AR	
Urticaria		2	2	AR, MG	Hives
Weight increased		2		AR	Weight gain
Drug administration error	1			UI	
Fatigue	1			AR, MG	Malaise
Myopia	1			AR, DI, MG	Blurred vision
Viral infection	1			AR, USP, MG	Sinusitis, Infection
Vision blurred	1			AR, DI, MG	Blurred vision

[1] May include duplicates

[2] BW = Boxed Warning, W/P = Warnings/Precautions, AR = Adverse Reactions, DI = Drug Interactions, OD = Overdosage, USP = Use in Specific Populations, PCI = Patient Counseling Information, MG = Medication Guide, DR = Disease-related, IR = Indication-related, UI = Uninformative

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/s/

KELLEY M SIMMS
10/18/2010

CINDY M KORTEPETER
10/18/2010

ANN WARD W MCMAHON
10/18/2010
I concur