Pediatric Focused Safety Review: Lamictal XR® (lamotrigine extended-release)

Pediatric Advisory Committee Meeting
December 7th, 2010

Virginia Elgin, M.D., FAAP; Medical Officer
Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Outline

• Background Information
• Pediatric Studies
• Pediatric Labeling Changes
• Additional Relevant Safety Labeling
• Drug Use Trends
• Adverse Events
• Summary
Background Drug Information
Lamictal® (Lamotrigine)

• **Original Market Approval:** December 27th, 1994.
  – Lamictal Chewable Dispersable Tablets (CD): August 24th, 1998
  – Lamictal Orally Disintegrating Tablets (ODT): May 8th, 2009

• **Boxed Warning:** August 24th, 1998
  – Serious, life-threatening, and fatal rashes in adults and pediatric patients

• **Pediatric Exclusivity Granted:** February 14, 2007
  – Efficacy and safety studies in 1 to 24 months; in ≥ 2 years

• **Labeled Formulations Include:** regular tablets, chewable tablets, and orally disintegrating tablets.
Background Drug Information
Lamictal® (Lamotrigine)

• **Current Indications Include:**
  – Adjunctive therapy of epilepsy in patients two years of age and older
  – Generalized tonic-clonic seizures
  – Partial seizures with or without secondary generalization
  – Patients with Lennox-Gastaut syndrome
  – Patients ≥ 16 years as monotherapy in selected individuals converting over from other therapeutic agents
  – Maintenance treatment of bipolar I disorder in patients ≥ 18 years.
Background Drug Information

Lamictal® Lamotrigine
November 18th 2008 PAC

- PAC supported recommendation from July AC regarding labeling for suicidality (Section 505(o)(4) of the FDCA
- Labeling change occurred April 23rd, 2009
- Suicidal behavior and ideation added to the Warnings and Precautions Section (5.5)
Background Drug Information

- **Drug**: Lamictal XR® (lamotrigine extended-release)
- **Formulation**: enteric coated tablets
- **Therapeutic Category**: antiepileptic drug (AED)
- **Sponsor**: Smithkline Beecham
Background Drug Information

Lamictal XR® (lamotrigine extended-release)

• **Original Market Approval:** May 29th, 2009.
• **Original Indication:**
  – Adjunctive therapy for partial seizures with or without secondary generalization in patients ≥ 13 years
Background Drug Information
Lamictal XR® (lamotrigine extended-release)

Labeling Updates

- **New Indication:** January 29th, 2010
  - Adjunctive therapy for primary generalized tonic-clonic seizures (PGTC) in patients ≥ 13 years (Section 1.1).
  - Dosing titration regimen includes new indication (Section 2.2)

- **New Dosage Strength:** April 14th, 2010
  - 300 mg tablets added to 25, 50, 100, 200 mg tablets (Section 3.1)
Background Pediatric Studies
Lamictal® XR (lamotrigine extended-release)

• 19 week double-blind, multi-center, randomized (1:1), placebo-controlled study in 143 patients 13 to 16 years of age, who had at least 3 primary generalized tonic-clonic seizures at baseline

• 19 week double-blind, multi-center, randomized (1:1), study in 236 patients ≥ 13 years (93% aged 16-65 years) for partial onset seizures with or without secondary generalization with a baseline of at least 8 partial seizures during an 8 week baseline period

• In both studies, patients received a fixed target dose of 200 to 500 mg a day and were allowed to take up to two other concomitant AEDs.
Background Pediatric Studies
Lamictal® XR (lamotrigine extended-release)

- IR formulation of Lamictal for the treatment of partial seizures in the 12-18 year range had over a 90% congruence of bioavailability with the XR formulation.
- The IR formulation was already approved for adults and pediatric patients in the 13 to 16 year age range.
- A requirement to study Lamictal XR in the 1 month to 13 year age range was waived since the IR and XR formulations exhibited similar Pharmacokinetic behavior and dosing information was adequately labeled.
Lamictal XR® (lamotrigine extended release)  
Additional Relevant Safety Labeling

SECTION 5: WARNINGS AND PRECAUTIONS:

• 5.1 Life-threatening serious rash or death  
  – Boxed Warning

• 5.2 Hypersensitivity:
  – Rash may not be present (fever, lymphadenopathy)
  – Discontinue if alternative etiology not determined

• 5.3 Multi-organ failure has occurred
Lamictal XR® (lamotrigine extended-release) Additional Relevant Safety Labeling

SECTION 5: WARNINGS AND PRECAUTIONS:

• **5.4** Blood dyscrasias; neutropenia, pancytopenia, thrombocytopenia

• **5.5** Suicidal behavior and ideation

• **5.6** Medication errors involving name confusion (see also Sections 3.2, 16, and 17.9)
Outpatient Utilization Data
Lamictal® (lamotrigine) All Formulations
May 2009 to April 2010

Source: SDI Vector One®: National. Extracted Sept 2010

• Approximately 9 million dispensed prescriptions and 1.5 million unique patients for all lamotrigine formulations:
  – Lamictal® (and generic lamotrigine), Lamictal® ODT, Lamictal® CD, and Lamictal® XR
  – 5% (414,947 prescriptions) patients aged 13-16 years
  – 3% (267,537 prescriptions) patients aged 8-12 years
  – 1% (93,707 prescriptions) patients aged 0-7 years
Outpatient Utilization Data
Lamictal XR® (lamotrigine extended-release)
May 2009 to April 2010
Source: SDI Vector One®: National. Extracted Sept 2010

- 75,000 prescriptions and 20,000 patients (<1% of the total lamotrigine Rx market)
- Pediatric patients (0-16 years)
  - 11,554 dispensed prescriptions (15%)
  - 2,600 patients (13%)
Dispensed Prescriptions: All Formulations

Figure 1: Total Number of Dispensed Prescriptions Through U.S. Outpatient Pharmacies for Lamotrigine Products, May 2009-April 2010

# Prescriptions Dispensed by Age: All Forms

| Table 1. Total Number of Dispensed Prescriptions Through U.S. Outpatient Retail Pharmacies for Lamotrigine Products by Age, May 2009-April 2010 Cumulative |
|---|---|---|
|  | **TRxs** | **Share** |
| **Total Market** | 8,988,733 | 100.0% |
| Age 0-7 | 93,707 | 1.0% |
| Chewable Tab (Lamictal CD) | 50,137 | 53.5% |
| Regular Tab (Lamictal and generic lamotrigine) | 38,859 | 41.5% |
| Soluble Tab (Lamictal ODT) | 4,056 | 4.3% |
| Long Acting (Lamictal XR) | 589 | 0.6% |
| Age 8-12 | 267,537 | 3.0% |
| Regular Tab (Lamictal and generic lamotrigine) | 214,083 | 80.0% |
| Chewable Tab (Lamictal CD) | 43,718 | 16.3% |
| Soluble Tab (Lamictal ODT) | 5,409 | 2.0% |
| Long Acting (Lamictal XR) | 4,148 | 1.6% |
| Age 13-16 | 414,947 | 4.6% |
| Regular Tab (Lamictal and generic lamotrigine) | 388,362 | 93.6% |
| Chewable Tab (Lamictal CD) | 15,317 | 3.7% |
| Long Acting (Lamictal XR) | 6,817 | 1.6% |
| Soluble Tab (Lamictal ODT) | 3,890 | 0.9% |
| Age 17+ | 8,212,339 | 91.4% |
| Regular Tab (Lamictal and generic lamotrigine) | 8,038,208 | 97.9% |
| Chewable Tab (Lamictal CD) | 65,466 | 0.8% |
| Long Acting (Lamictal XR) | 63,162 | 0.8% |
| Soluble Tab (Lamictal ODT) | 38,226 | 0.5% |
| Age UNSPEC | 202 | 0.0% |
| Regular Tab (Lamictal and generic lamotrigine) | 178 | 87.9% |
| Chewable Tab (Lamictal CD) | 25 | 12.1% |

Patients Receiving a Prescription: Lamotrigine All Forms

Table 3. Total Number of Patients Receiving a Prescription Through U.S. Outpatient Retail Pharmacies for Lamotrigine Products by Age, May 2009-April 2010 Cumulative

<table>
<thead>
<tr>
<th>Age</th>
<th>Patients N</th>
<th>Share %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grand Total</strong></td>
<td>1,548,312</td>
<td>100.00%</td>
</tr>
<tr>
<td>Age 0-7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chewable Tab (Lamictal CD)</td>
<td>15,633</td>
<td>1.01%</td>
</tr>
<tr>
<td>Regular Tab (Lamictal and generic lamotrigine)</td>
<td>9,043</td>
<td>57.85%</td>
</tr>
<tr>
<td>Soluble Tab (Lamictal ODT)</td>
<td>8,210</td>
<td>52.52%</td>
</tr>
<tr>
<td>Long Acting (Lamictal XR)</td>
<td>1,263</td>
<td>8.08%</td>
</tr>
<tr>
<td><strong>Age 8-12</strong></td>
<td>43,772</td>
<td>2.83%</td>
</tr>
<tr>
<td>Regular Tab (Lamictal and generic lamotrigine)</td>
<td>37,184</td>
<td>84.95%</td>
</tr>
<tr>
<td>Chewable Tab (Lamictal CD)</td>
<td>8,661</td>
<td>19.79%</td>
</tr>
<tr>
<td>Soluble Tab (Lamictal ODT)</td>
<td>1,608</td>
<td>3.67%</td>
</tr>
<tr>
<td>Long Acting (Lamictal XR)</td>
<td>953</td>
<td>2.18%</td>
</tr>
<tr>
<td><strong>Age 13-16</strong></td>
<td>78,501</td>
<td>5.07%</td>
</tr>
<tr>
<td>Regular Tab (Lamictal and generic lamotrigine)</td>
<td>74,973</td>
<td>95.51%</td>
</tr>
<tr>
<td>Chewable Tab (Lamictal CD)</td>
<td>3,839</td>
<td>4.89%</td>
</tr>
<tr>
<td>Long Acting (Lamictal XR)</td>
<td>1,591</td>
<td>2.03%</td>
</tr>
<tr>
<td>Soluble Tab (Lamictal ODT)</td>
<td>1,352</td>
<td>1.72%</td>
</tr>
<tr>
<td><strong>Age 17+</strong></td>
<td>1,427,447</td>
<td>92.19%</td>
</tr>
<tr>
<td>Regular Tab (Lamictal and generic lamotrigine)</td>
<td>1,401,139</td>
<td>98.16%</td>
</tr>
<tr>
<td>Chewable Tab (Lamictal CD)</td>
<td>24,314</td>
<td>1.70%</td>
</tr>
<tr>
<td>Long Acting (Lamictal XR)</td>
<td>17,455</td>
<td>1.22%</td>
</tr>
<tr>
<td>Soluble Tab (Lamictal ODT)</td>
<td>13,840</td>
<td>0.97%</td>
</tr>
</tbody>
</table>

Pediatric Lamictal XR® (lamotrigine extended-release) Prescriptions

Table 2. Total Number of Patients Receiving a Prescription for Through U.S. Outpatient Retail Pharmacies for Lamictal XR by Age, May 2009-April 2010 Cumulative

<table>
<thead>
<tr>
<th>Age</th>
<th>Patients N</th>
<th>Share %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-16</td>
<td>2,634</td>
<td>12.9%</td>
</tr>
<tr>
<td>0-7</td>
<td>137</td>
<td>5.2%</td>
</tr>
<tr>
<td>8-12</td>
<td>958</td>
<td>36.4%</td>
</tr>
<tr>
<td>13-16</td>
<td>1,615</td>
<td>61.3%</td>
</tr>
<tr>
<td>Age 17+</td>
<td>17,890</td>
<td>87.8%</td>
</tr>
</tbody>
</table>

Lamictal XR Grand Total | 20,384 | 100.0% |

Prescribing Specialties for Lamotrigine Products
May 2009 to April 2010
Source: SDI Vector One®: National. Extracted Sept 2010

- **Regular Tab (Lamictal and generic):** Psych (50%) and Neuro (17%)
- **Lamictal CD:** Neuro (43%) and Psych (19%)
- **Lamictal XR:** Neuro (68%)
- **Lamictal ODT:** Psych (58%) and Neuro (16%)
Diagnoses Associated with Lamotrigine Products
May 2009 to April 2010
Source: SDI Vector One®: National. Extracted Sept 2010

• For all lamotrigine formulations:
  – top diagnoses were “Epilepsy NOS” and “Bipolar Affective NOS” (regardless of age)
# Top 5 Diagnoses Associated with Lamotrigine Products

## Table 5. Top 5 Diagnosis Associated with the use of Lamotrigine Products by Age as Reported by Office-Based Physician Practices, May 2009 to April 2010

<table>
<thead>
<tr>
<th>Total Market</th>
<th>05/2009-04/2010</th>
<th>Share%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamictal and generic lamotrigine</td>
<td>3,605</td>
<td>96.8%</td>
</tr>
<tr>
<td>Age 0-7</td>
<td>31</td>
<td>1.0%</td>
</tr>
<tr>
<td>3459 EPILEPSY NOS</td>
<td>14</td>
<td>43.9%</td>
</tr>
<tr>
<td>3093 ADJUST REACT-CONDUCT DIS</td>
<td>6</td>
<td>20.2%</td>
</tr>
<tr>
<td>2999 EARLY CHILD PSYCHOSIS NOS</td>
<td>6</td>
<td>19.1%</td>
</tr>
<tr>
<td>7803 CONVULSIONS</td>
<td>5</td>
<td>16.7%</td>
</tr>
<tr>
<td>Age 8-12</td>
<td>67</td>
<td>1.9%</td>
</tr>
<tr>
<td>3459 EPILEPSY NOS</td>
<td>44</td>
<td>63.7%</td>
</tr>
<tr>
<td>3450 GEN NONCONVULS EPILEPSY</td>
<td>7</td>
<td>10.7%</td>
</tr>
<tr>
<td>3455 PARTIAL EPILEPSY NEC</td>
<td>6</td>
<td>9.1%</td>
</tr>
<tr>
<td>2967 BIPOLAR AFFECTIVE NOS</td>
<td>6</td>
<td>8.8%</td>
</tr>
<tr>
<td>7803 CONVULSIONS</td>
<td>5</td>
<td>8.4%</td>
</tr>
<tr>
<td>Age 13-16</td>
<td>94</td>
<td>3.0%</td>
</tr>
<tr>
<td>2967 BIPOLAR AFFECTIVE NOS</td>
<td>21</td>
<td>22.3%</td>
</tr>
<tr>
<td>2969 AFFECT PSYCHOSES NEC/NOS</td>
<td>20</td>
<td>20.9%</td>
</tr>
<tr>
<td>3459 EPILEPSY NOS</td>
<td>17</td>
<td>17.7%</td>
</tr>
<tr>
<td>3098 OTHER ADJUST REACTION</td>
<td>11</td>
<td>12.0%</td>
</tr>
<tr>
<td>3000 ANXIETY STATES</td>
<td>9</td>
<td>9.3%</td>
</tr>
<tr>
<td>All Others</td>
<td>17</td>
<td>17.9%</td>
</tr>
<tr>
<td>Age 17+</td>
<td>3,239</td>
<td>89.8%</td>
</tr>
<tr>
<td>2967 BIPOLAR AFFECTIVE NOS</td>
<td>1,009</td>
<td>31.2%</td>
</tr>
<tr>
<td>2968 MANIC-DEPRESSIVE NEC/NOS</td>
<td>588</td>
<td>18.2%</td>
</tr>
<tr>
<td>3459 EPILEPSY NOS</td>
<td>256</td>
<td>7.9%</td>
</tr>
<tr>
<td>7803 CONVULSIONS</td>
<td>175</td>
<td>5.4%</td>
</tr>
<tr>
<td>3110 DEPRESSIVE DISORDER NEC</td>
<td>144</td>
<td>4.4%</td>
</tr>
<tr>
<td>All Others</td>
<td>1,006</td>
<td>32.1%</td>
</tr>
<tr>
<td>Age UNSPEC</td>
<td>175</td>
<td>4.9%</td>
</tr>
</tbody>
</table>
## Top 5 Diagnoses Associated with Lamotrigine Products Cont.

<table>
<thead>
<tr>
<th>Lamictal XR</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 17+</td>
<td>80</td>
<td>2.2%</td>
</tr>
<tr>
<td>3459 EPILEPSY NOS</td>
<td>21</td>
<td>26.1%</td>
</tr>
<tr>
<td>2967 BIPOLAR AFFECTIVE NOS</td>
<td>18</td>
<td>22.0%</td>
</tr>
<tr>
<td>7803 CONVULSIONS</td>
<td>12</td>
<td>15.0%</td>
</tr>
<tr>
<td>3455 PARTIAL EPILEPSY NEC</td>
<td>12</td>
<td>14.5%</td>
</tr>
<tr>
<td>2963 DEPR PSYCH, RECUR EPISOD</td>
<td>5</td>
<td>6.4%</td>
</tr>
<tr>
<td>All Others</td>
<td>12</td>
<td>16.1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lamictal ODT</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 0-7</td>
<td>32</td>
<td>0.9%</td>
</tr>
<tr>
<td>3459 EPILEPSY NOS</td>
<td>3</td>
<td>9.3%</td>
</tr>
<tr>
<td>Age 17+</td>
<td>29</td>
<td>90.7%</td>
</tr>
<tr>
<td>2967 BIPOLAR AFFECTIVE NOS</td>
<td>11</td>
<td>36.9%</td>
</tr>
<tr>
<td>2968 MANIC-DEPRESSIVE NEC/NOS</td>
<td>9</td>
<td>30.6%</td>
</tr>
<tr>
<td>2965 BIPOLAR AFFECT, DEPRESS</td>
<td>5</td>
<td>17.8%</td>
</tr>
<tr>
<td>3140 ATTENTION DEFICIT DIS</td>
<td>4</td>
<td>14.7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lamictal CD</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age UNSPEC</td>
<td>6</td>
<td>0.2%</td>
</tr>
<tr>
<td>3459 EPILEPSY NOS</td>
<td>6</td>
<td>100.0%</td>
</tr>
</tbody>
</table>


Lamotrigine Product by Age Dx4 9-10-10.xls
### Crude Counts for Adverse Events Lamictal® XR (lamotrigine extended-release)
**May 29, 2009 to June 30th, 2010**

<table>
<thead>
<tr>
<th>Crude counts*</th>
<th>All reports (US)</th>
<th>Serious** (US)</th>
<th>Death (US)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total All Ages</td>
<td>98 (98)</td>
<td>39 (39)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>- Adults (≥ 17)</td>
<td>57 (57)</td>
<td>21 (21)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>- Pediatrics (0-16 yrs)</td>
<td>5 (5)</td>
<td>3 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>- Unknown Age</td>
<td>36 (36)</td>
<td>15 (15)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*may include duplicates

**Serious AEs per regulatory definition (CFR 314.80) include death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events
Case Characteristics of Lamictal® XR  
(lamotrigine extended-release)  
May 29th 2009 to June 30th, 2010  
(n= 3 serious; n= 2 non-serious)  

- 5 reported adverse events reported in children 0-16 years represent 5% of the total (5/98); all US:  
  - All treated for seizures  
  - Age range 7-16 years  
  - Dosing Range: 25-500 mg
Case Characteristics of Lamictal® XR
(lamotrigine extended-release)
May 29th 2009 to June 30th, 2010

- There were no reported cases of hepatotoxicity, aseptic meningitis, or life-threatening rashes such as Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis
Lamictal® XR
Serious Labeled Adverse Events (lamotrigine extended-release)
May 29th 2009 to June 30th, 2010

• 10 year old male on Depakote, took 25 mg Lamictal XR daily instead of every other day
• Developed rash and fever
• Depakote and Lamictal XR were discontinued
• No further history
Lamictal® XR
Serious Labeled Adverse Events (lamotrigine extended-release)
May 29th 2009 to June 30th, 2010

• 16 year old female on Zonegran (zonisamide)

• Began lamotrigine at 500 mg and Zonegran was tapered with plans to switch to Lamictal XR monotherapy

• Experienced a breakthrough seizure
Lamictal® XR
Serious Labeled Adverse Events (lamotrigine extended-release)
May 29th 2009 to June 30th, 2010

• 14 year old female on Keppra (leviracetam)
• Patient started on either 50 or 100 mg daily Lamictal XR
• Experienced seizures NOS and fatigue going from 50 to 100 mg but actual starting dose not clear from report
Lamictal® XR
(lamotrigine extended-release)
Non-Serious Labeled Adverse Event May 29th
2009 to June 30th, 2010

• 7 year old female with no reported history of concomitant medication
• Started Lamictal XR 50 mg bid
• Experienced worsening of nearsightedness and blurry vision
• Outcome unknown
Lamictal® XR
(lamotrigine extended-release)
Non-Serious Un-Labeled Adverse Event
May 29th 2009 to June 30th, 2010

- 15 year old female on folic acid and clonazepam.
- Started Lamictal XR at 300 mg daily for epilepsy (100 mg am 200 mg pm)
- Experienced bruxism
- Lamictal XR continued as of time of reporting with no resolution
Crude Counts Lamictal® XR, CD, and ODT with Serious Outcomes
May 29, 2009 to June 30th, 2010

<table>
<thead>
<tr>
<th></th>
<th>Lamictal XR</th>
<th>Lamictal CD</th>
<th>Lamictal ODT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-7 Years</td>
<td>0</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>8-12 Years</td>
<td>1</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>13-16 Years</td>
<td>2</td>
<td>18</td>
<td>4</td>
</tr>
<tr>
<td>Age Unknown</td>
<td>0</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>63</td>
<td>20</td>
</tr>
</tbody>
</table>

*may include duplicates
**Serious AEs per regulatory definition (CFR 314.80) include death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events
<table>
<thead>
<tr>
<th>PT</th>
<th>Count</th>
<th>Drug name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxic Shock Syndrome(^4)</td>
<td>4</td>
<td>“Lamictal CD tablets”</td>
</tr>
<tr>
<td>Autism</td>
<td>3</td>
<td>Lamictal CD tablets</td>
</tr>
<tr>
<td>Hypernatremia(^4)</td>
<td>3</td>
<td>“Lamictal CD tablets”</td>
</tr>
<tr>
<td>Lactose intolerance</td>
<td>3</td>
<td>Lamictal CD tablets</td>
</tr>
<tr>
<td>Cyanosis neonatal(^4)</td>
<td>2</td>
<td>“Lamictal CD tablets”</td>
</tr>
</tbody>
</table>

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.
Non-duplicated Cases of Serious Unlabeled Adverse Events
Lamictal CD
3 Patients
Children 0-16 Years

• N =1 each; toxic shock and hypernatremia
• N =1 each; autism and lactose intolerance
• N = 1; neonatal cyanosis
Serious Unlabeled Events
Pediatric Patients (0-16) Lamictal CD
May 29th, 2009 to June 30th, 2010
Toxic Shock Syndrome (n=1) and
Hypernatremia (n=1)

- 11 year old female on sodium valproate who developed hair loss
- Lamotrigine CD started with plan to wean sodium valproate
- Developed on Day 13 rash, rhabdomyolysis, hypernatremia, toxic shock syndrome, and multi-organ failure; both seizure medications stopped
- Full recovery post hospitalization; sodium valproate restarted
- Dermatologists later concluded it was Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS); AKA Multi-Organ Hypersensitivity
Serious Unlabeled Events in Pediatric Patients (0-16)
Lamictal CD
May 29th, 2009 to June 30th, 2010
Autism (n=1) and Lactose Intolerance (n=1)

- 14 year old with autism and a history of fungal infections and lactose intolerance on an anti-candida diet and nutritional supplements
- Taking Lamictal CD 125 mg/day and phenytoin 340 mg/day for seizures that began in 2005
- Unknown when autism was diagnosed
- Physician comments autism due to gut dysbacteriosis and not lamotrigine
Serious Unlabeled Events in Pediatric Patients (0-16) Lamictal CD
May 29th, 2009 to June 30th, 2010
Neonatal Cyanosis (n=1)

• A neonate’s mother was receiving 875 mg/day during her pregnancy with a 25 mg/week titration down post-partum at the time of the report.
• Normal dosing is 200-500 mg; depends on patient and use of concomitant AEDs
• Clearance of Lamictal during pregnancy may increase from 65 to as high as 300%
Serious Unlabeled Events in Pediatric Patients (0-16)
Lamictal CD
May 29th, 2009 to June 30th, 2010
Neonatal Cyanosis (n=1) Cont.

• 16 day old breast-fed male had a brief episode of apnea and then 3 hours later developed cyanosis

• 6 minutes of chest compressions resulted in normal color with spontaneous respirations*

Serious Unlabeled Events in Pediatric Patients (0-16) Lamictal CD  
May 29th, 2009 to June 30th, 2010  
Neonatal Cyanosis (n=1) Cont.

• His serum level was 4.87mcg/mL  
  – Proposed pediatric therapeutic range is 1- 5 mcg/mL  
  – Actual neonatal therapeutic range is unknown  
• Breastfeeding was discontinued DOL 17 and the patient had an uneventful recovery  
• Current labeling (Section 8.3) states: “Preliminary data indicate that lamotrigine passes into human milk. Because the effects on the infant by this route are unknown, breastfeeding while taking LAMICTAL XR is not recommended.”
Pediatric Maternal Health Staff Review of Lamotrigine and Breast-feeding

• Lamotrigine is metabolized predominantly by hepatic glucuronidation and is renally eliminated.
• Maternal lamotrigine serum levels and half-life (6-103 hours) vary widely between patients because of genetic differences in glucuronidation mainly due to different isoenzymes and the use of concomitant medications that either induce or inhibit glucuronidation.
Pediatric Maternal Health Staff Review of Lamotrigine and Breast-feeding

- Infants have relatively high plasma levels, averaging 30 to 35% of maternal serum levels.
- Glucuronidation needed to metabolize lamotrigine is not mature in infants until they reach 2 to 6 months of age.
- Neonates have immature renal excretion; normal eGFR takes 6 months to 2 years to develop
Pediatric Maternal Health Staff Review of Lamotrigine and Breast-feeding

• The safety of lamotrigine has not been systematically assessed in neonates, infants, or in children <2 years of age.

• The approved pediatric lamotrigine starting dose in patients 2 to 12 years of age is 0.15 to 1.2 mg/kg/day and usual maintenance dose is 1 to 15 mg/kg/day, depending on concomitant medications.

• The lamotrigine relative infant dose (RID) was calculated at less than 10% in a few of the small studies from the literature reviewed; however, the theoretical infant doses used in these RID calculations, generally fell within or above the labeled therapeutic doses for children 2 to 12 years of age.
Pediatric Maternal Health Staff Review of Lamotrigine and Breast-feeding

• Despite the high infant lamotrigine doses received through human milk, there has been only one serious adverse reaction reported in a human milk-fed infant.

• Reports are limited and no data exists on the long-term neuropsychological and developmental outcomes in infants exposed to lamotrigine through human milk (or in-utero).
Summary Pediatric Focused Safety Review
Lamictal® XR (lamotrigine extended-release)

• This completes the pediatric focused safety review.
• Safety data from PREA studies have been incorporated into the label.
• FDA will continue to monitor adverse events associated with breastfeeding and routine monitoring
• Please comment on the following options:
  -- Continue monitoring for additional breastfeeding-associated cases in infants before making any labeling change
  -- Revise labeling to include lactation data from the literature to better inform lactation risk/benefit decision making
  -- Other recommendations?
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Stephanie N. Keefe

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Lisa L. Mathis, USPHS, M.D.
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Jeanine Best, MSN, RN, PNP
Karen Feibus, M.D. MPH

DNP
Russell Katz, M.D.
Norman Hershkowitz, M.D.
Steven Dinsmore, M.D.
Kun Jin, Ph.D.
Xiang Ling, Ph.D.
Angela Men, M.D.
Ta-Chen Wu, Ph.D.
Robbin Nighswander, R.Ph.
Stephanie N. Keefe

OPT
Judith Cope, M.D., MPH
Suzanne Malli, BA, BSN
Dianne Murphy, M.D.
Amy Odegaard, MPH
Pam Weinel, MS, MBA

OSE
Hina Mehta, PharmD
Grace Chai, PharmD
Laura Governale, PharmD, MBA

DEPI
DPV1
Ann W. McMahon, M.D., MS
Cindy Kortepeter, PharmD
Kelly M. Simms, PharmD, BCPS