

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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SUBJECT: 1-year Post-Pediatric Exclusivity Postmarketing Adverse Event Review  
Drug: Oxcarbazepine (Trileptal™) NDA# 21-014 and 21-285  
Pediatric Exclusivity Approval Date: March 2, 2005

## 1.0 Executive Summary

The AERS database was searched for reports of adverse events (serious and non-serious) occurring with the use of oxcarbazepine (Trileptal™) in pediatric patients. Up to the "data lock" date of April 2, 2006, AERS contained 2,482 reports for oxcarbazepine (Trileptal™) (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric cases represent approximately 16.5 % of the total (409/2,482).

DDRE was asked to focus on the 1-year period following the approval of pediatric exclusivity, March 2, 2005 to March 2, 2006. We used an AERS data lock date of April 2, 2006 to allow time for reports received up to March 2, 2006 to be entered into AERS. During the first 13 months after pediatric exclusivity was granted, AERS received a total of 493 reports (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric cases represent

approximately 18% of the total number of cases (88/493). We will refer to this 13-month interval as the pediatric exclusivity period in the remainder of this review.

#### Case Series Summary

We identified and reviewed 84 unduplicated AERS cases (reported during the pediatric exclusivity period) of various adverse events associated with Trileptal for children under the age of 17 years, including one fatal case. A second search of AERS was conducted for Trileptal cases with fatal outcomes reported in children (age 0 thru 16 years) from the approval date of January 14, 2000 through March 2, 2005 and 12 additional fatal cases were identified (for a total of 13 pediatric fatalities entered into the AERS database from January 14, 2000 through April 2, 2006).

#### Fatal cases

Of the 13 fatal cases, one case involved a 15 year old male with no known history of psychiatric disorders or prior suicide attempts during eight months of Trileptal use. He received no concomitant drugs. He self-inflicted a fatal gunshot wound to his chest. Of note, cases of suicide are currently under review by the Division of Neurology Products, and the sponsor for Trileptal. We will inform you of the findings when the information becomes available.

One fatal case was reported during the pediatric exclusivity period. This case (from China, 2005) involved a six year old who “died due to rhabdomyolysis” (CPK = 100,000 units unspecified). This case contained sparse information and did not provide details on whether the child complained of muscle weakness, was positive for myoglobinuria, or experienced renal failure. Also, it is unknown what other factors preceded the development of rhabdomyolysis including seizure activity (e.g. status epilepticus is known to be associated with rhabdomyolysis).

The remaining 11 fatal cases, although coincident with Trileptal therapy, involved other suspect medications and/or an underlying seizure disorder that may have contributed to and/or was secondary to the cause of death. Furthermore, some cases either lacked the clinical details necessary for a thorough evaluation or reported the cause of death as unknown.

#### Non-fatal cases

During the pediatric exclusivity period, there were 83 nonfatal pediatric cases of various adverse events that were stratified as either unlabeled-unexpected (52) or labeled-expected (31). The 52 cases of various unlabeled events included one case of an anaphylactic reaction that occurred 30 minutes post dose in a four year old male. A full evaluation of similar AERS reports in pediatric and adult patients is forthcoming in a separate DDRE review.

Of the remaining 51 cases of unlabeled-unexpected events, there were too few compelling cases to characterize any one adverse event as a potential safety signal. Although the events occurred in pediatric patients, the described events were similar to those observed in adults, excluding events occurring in utero.

There were 31 cases of various events associated with Trileptal that are listed or implied in the current product label. The labeling status for these adverse events included Warnings for serious skin reactions (including SJS) – 7, and hyponatremia -1, and Precautions for multiple organ system hypersensitivity - 2. The remaining 21 various events are described in the postmarketing section of the label in a line listing. There were too few cases of any one event to warrant more prominence in the label.

Table of Contents

<b>2.0</b>	<b>Products, Indications, Pediatric Labeling and Pediatric Filing History.....</b>	<b>p. 4</b>
<b>2.1</b>	<b>Trileptal Products .....</b>	<b>p. 4</b>
<b>2.2</b>	<b>Trileptal approved Indication .....</b>	<b>p. 4</b>
<b>2.3</b>	<b>Trileptal Pediatric Labeling .....</b>	<b>p. 4</b>
<b>2.4</b>	<b>Pediatric Filing History .....</b>	<b>p. 4</b>
<b>3.0</b>	<b>AERS Search Results: Trileptal .....</b>	<b>p. 5</b>
<b>3.1</b>	<b>Count of Reports .....</b>	<b>p. 5</b>
<b>3.2</b>	<b>Count of Reports.....</b>	<b>p. 6</b>
<b>4.0</b>	<b>Postmarketing Review of All Pediatric Adverse Event Reports received during the one-year after a drug receives pediatric market exclusivity .....</b>	<b>p. 6</b>
<b>4.1</b>	<b>Case Characteristics/Demographics .....</b>	<b>p. 6</b>
<b>4.2</b>	<b>Summary of Cases received during the one-year post-pediatric exclusivity period ...</b>	<b>p. 7</b>
<b>4.2.1</b>	<b><u>Fatal cases</u> .....</b>	<b>p. 7</b>
<b>4.2.2</b>	<b><u>Non-fatal cases</u>.....</b>	<b>p. 9</b>
	4.2.2.1 Non-fatal unlabeled/unexpected cases .....	<b>p. 9</b>
	4.2.2.1.1 Cardiac events .....	<b>p. 10</b>
	4.2.2.1.2 Dental events .....	<b>p. 10</b>
	4.2.2.1.3 Endocrine events .....	<b>p. 10</b>
	4.2.2.1.4 Hematologic events .....	<b>p. 10</b>
	4.2.2.1.5 Hepatobiliary events .....	<b>p. 11</b>
	4.2.2.1.6 Immune system events .....	<b>p. 11</b>
	4.2.2.1.7 In utero exposure .....	<b>p. 11</b>
	4.2.2.1.8 Electrolyte conditions .....	<b>p. 12</b>
	4.2.2.1.9 Musculoskeletal events .....	<b>p. 12</b>
	4.2.2.1.10 Neurologic events .....	<b>p. 12</b>
	4.2.2.1.11 Ophthalmic events .....	<b>p. 12</b>
	4.2.2.1.12 Psychiatric events .....	<b>p. 13</b>
	4.2.2.1.13 Renal events .....	<b>p. 13</b>
	4.2.2.1.14 Vascular events .....	<b>p. 13</b>
	4.2.2.1.15 General events .....	<b>p. 13</b>
	4.2.2.2 Non-fatal labeled/expected cases .....	<b>p. 14</b>
<b>5.0</b>	<b>Conclusion .....</b>	<b>p. 14</b>
	<b>Appendix I: Pediatric Dosing .....</b>	<b>p. 15</b>
	<b>Appendix II: Limitations of AERS .....</b>	<b>p. 17</b>

## **2.0 Products, Indications, Pediatric Labeling, and Pediatric Filing History:**

### **2.1 Trileptal Products:**

Trileptal™ (oxcarbazepine), NDA # 21-285 and 21-014 which is sponsored by Novartis Pharmaceuticals Corporation, and U.S. Approval on January 14, 2000, is formulated in:

Tablets: 150, 300, and 600 mgs, and oral suspension: 300 mg/5ml.

### **2.2 Trileptal approved Indication**

Trileptal is indicated as monotherapy or adjunctive therapy in the treatment of partial seizures in adults, and as monotherapy in the treatment of partial seizures in children aged 4 years and above with epilepsy, and as adjunctive therapy in children aged 2 years and above with epilepsy.

### **2.3 Trileptal Pediatric Labeling**

Warnings: hyponatremia, carbamazepine cross-reaction hypersensitivity, serious dermatological reactions, and rebound seizure effect due to abrupt withdrawal of antiepileptic drugs.

Precautions: cognitive/neuropsychiatric adverse events and multi-organ system hypersensitivity.

Pregnancy category: C

**Pediatric Use: Trileptal has been given to about 623 patients between the ages of 3- 17 years in controlled clinical trials (185 treated as monotherapy) and about 615 patients between the ages of 3-17 years in other trials.** Pediatric Dosing: See Appendix I

### **2.4 Pediatric Filing History**

A formal Written Request for studies of oxcarbazepine (Trileptal™) in pediatric patients, ages 1 month to 16 years, was issued to Novartis on February 28, 2000. The sponsor completed two studies, monotherapy (#2339) and adjunct therapy (#2340) that were reviewed by FDA.<sup>1</sup> In general, the monotherapy trial failed the primary endpoint, and the adjunct therapy trial was successful. The findings revealed the following:

Monotherapy trial (2339): The comparison results across trials indicated that the study was not adequately designed and conducted. The major deficiencies include the short duration of the study and lack of documentation of the seizure rate at baseline. These deficiencies render the study results uninterpretable. However, this study did provide information for comparison of pharmacokinetics (PK) between children and adults.

Adjunct trial (2340): The comparison between the current and previous studies indicates that similar Trileptal concentrations are achieved among different studies. The dosing utilized in this study is considered adequate. Given the higher body weight adjusted clearance in 1 month to < 4 years old children, a higher mg/kg dose should be considered in children with body weight less than 20 kg.

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<sup>1</sup> FDA Clinical Pharmacology and Biopharmaceutics review by John Duan, Ph.D.; Pediatric supplement submitted 12/13/04

Because the studies fulfilled the requirement of the Written Request, pediatric exclusivity was granted on March 2, 2005. Based on the study data, labeling changes were approved to extend indications for Trileptal as adjunctive therapy with new dosing recommendations to treat partial seizures in children ages 2 - <4 years<sup>2</sup>.

### 3.0 AERS Search Results: Trileptal

3.1 **Count of Reports:** AERS Search including all sources - U.S. & foreign from January 14, 2000 through April 2, 2006 (Table 1).

<b>Table 1: Crude counts* of AERS Reports for all sources from Marketing Approval Date (January 14, 2000- to April 2, 2006) (US counts in parentheses)</b>			
	<b>All reports (US)</b>	<b>Serious** (US)</b>	<b>Death (US)</b>
Adults (≥ 17 yrs.)	1,653 (834)	1,465 (654)	123 (66)
Pediatrics (0-16 yrs.)	409 (242)	344 (177)	21 (5)
Age unknown (Null values)	416 (266)	351 (202)	12 (5)
<b>Total</b>	<b>2,482 (1,346)</b>	<b>2,164 (1,037)</b>	<b>156 (76)</b>
* May include duplicates			
** Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other. One report may indicate more than one outcome.			

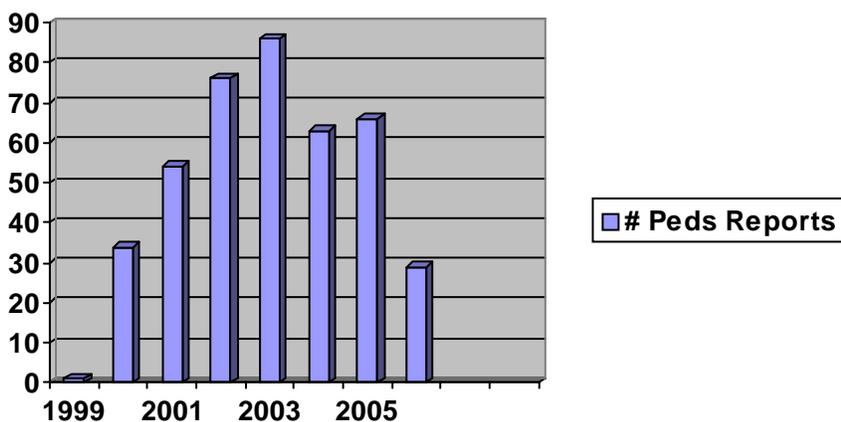


Figure 1: Reporting trend for pediatric reports from January 14, 2000 through April 2006:

<sup>2</sup> According to John Duan, Ph.D., there was insufficient study data to support labeling for children < 2 years old.

**3.2 Count of Reports:** AERS Search including all sources - U.S. & foreign from March 2, 2005 through April 2, 2006 (Table 2).

<b>Table 2: Crude counts* of AERS Reports for all sources from date Pediatric Exclusivity was granted (March 2, 2005 - April 2, 2006) (US counts in parentheses)</b>			
	<b>All reports (US)</b>	<b>Serious** (US)</b>	<b>Death (US)</b>
Adults (≥ 17 yrs.)	308 (182)	299 (176)	33 (27)
Pediatrics (0-16 yrs)	88*** (59)	82 (53)	1 (0)
Age unknown (Null Values)	95 (64)	88 (58)	4 (2)
<b>Total</b>	<b>493 (307)</b>	<b>471 (289)</b>	<b>38 (29)</b>
<p>* May include duplicates            ** Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other. One report may report more multiple outcomes.            *** Crude count. Actual count of reports is 84.</p>			

**4.0 Postmarketing Review of All Pediatric Adverse Event Reports received during the one-year after a drug receives pediatric market exclusivity.**

**4.1 Case Characteristics/Demographics (84)**

<b>Table 3: Characteristics of pediatric cases reported during the pediatric exclusivity period March 6, 2005 through April 6, 2006 (n=84)</b>	
Gender [n=83]	Male: 50 Female:33
Age [n=82]	0- <1 month (2) 1 month <2 yrs (3) 2-5 yrs - (15) 6-11 yrs – (32) 12-16 yrs - (30) Average age = 10 years Median age = 10 years Range = 2 days – 16years
Origin [n=83]	US - 55, Foreign – 28,
Event date [n=84]	2005 - 59 ; 2006 - 25
Daily dose [n=53]	Average – 933 mg Median – 600 mg Range: 60 mg – 6,750 mg (latter Trileptal dose related to thyroid hormone level abnormality.)
Duration of therapy [n=30]	Average – 177 days (6 months) Median – 30 days (1 month)

**Table 3: Characteristics of pediatric cases reported during the pediatric exclusivity period March 6, 2005 through April 6, 2006 (n=84)**

	Range: 30 minutes – 5 years
Indications [n=63]	Seizure – 40, Bipolar disorder – 6, Affective disorder – 5, ADHD – 4, no indication for fetus in utero w/ passive exposure – 4, Abnormal behavior – 2, Labile mood -1, and opposition defiant disorder - 1
Outcomes [n= 84]	Death - 1, Life-Threatening - 10, Hospitalization – 23, Disability - 11, Congenital Anomaly - 1, Medically significant – 21, other (as non-serious) - 19
A report may have more than one outcome.	

## 4.2 Summary of Cases received during the one-year post-pediatric exclusivity period

From an AERS raw report count of 88, after the removal of duplicate cases, 84 unduplicated pediatric cases remained for review. One case reported a fatal outcome. The entire case series of various adverse reactions is further stratified into fatal cases and non-fatal cases.

### 4.2.1 Fatal cases

A single case with death as an outcome was identified during the duration of interest and is summarized below.

In a case (ISR#4823835, China, 2005) under litigation, a six year old of unknown gender “died due to rhabdomyolysis.” The patient initiated Trileptal at a dose of 150 mg daily and subsequently increased it to 300 mg daily for nine days to manage epilepsy. The patient developed a fever (39 – 40 °C) that required hospital admission. Laboratory findings revealed elevated values for CPK (100,000 units unspecified). The patient was diagnosed with rhabdomyolysis and later died. This case contained sparse information and did not provide details on whether the child complained of muscle weakness, was positive for myoglobinuria, or experienced renal failure. Also, it is unknown what other factors preceded the development of rhabdomyolysis including any seizure activity (e.g. status epilepticus is known to be associated with rhabdomyolysis).<sup>3</sup>

To identify all fatal pediatric cases for Trileptal, a second AERS search was conducted utilizing dates from market approval (January 14, 2000) through March 2, 2005. This search identified 12 unduplicated cases in children under the age of 17 years.

A summary of the cases follow (n=12):

- There were four deaths secondary to seizure activity which was the indication for treatment. The first case (ISR#3566244, US, 2000) reported the death of an 11 year old male due to asphyxiation. The patient’s history included nocturnal seizures. The patient experienced an evening seizure during which he became wedged between the bed and night stand, and suffocated. The second case (ISR#3821853, France, 2001) reported a nine year old patient who experienced several seizures (status epilepticus) during the night and died. The third case

<sup>3</sup> Holland-Frei Cancer Medicine – 6<sup>th</sup> Ed. (2003), electronic source.

(ISR#3900658, US, 2002) occurred in a 15 year old female with recent seizure activity that induced a comatose state. Due to prolonged CPR measures, the patient was classified as DNR and died of a cardiac arrest. The last case (ISR#3464478, Germany, 2000) of multiple organ system disorders characterized as metabolic acidosis, rhabdomyolysis, and hypertriglyceridemia reported a 10 year old male with a medical history of mental retardation and cryptogenic therapy-resistant focal epilepsy. The patient experienced status epilepticus and subsequently died from multiple organ system failure.

- There were two cardiac cases temporally related to a regimen with multiple drugs including Trileptal, which reported either cardiac arrest or myocarditis.

In one case (ISR#4218076, France, 2003), a 16 year old received a poly-medication regimen that included two suspect drugs, Lamictal and Trileptal, within two months of the event. The patient experienced fatal cardiac arrest on 16Jul03 subsequent to a dose increase of Lamictal on 07Jul03. The French authority deemed the causal relationship as unlikely.

The other case (ISR#4414936, Spain, 2004) in an 11 year old female who received multiple suspect medication experienced myocarditis, which was serology negative for microorganisms.

- There was one case of suicide. A case (ISR#4592769, US, February 2005) of a 15 year old male who had never attempted suicide and a family history positive for depression, schizophrenia, and drug abuse committed suicide. The patient received eight months of Trileptal starting on 26Feb2003 at doses of 300 mg that was titrated to 1200 mg daily to treat complex partial seizures. The patient was not taking any other concomitant medications, and the presence of only Trileptal in the blood was confirmed at autopsy. The patient developed psychosis that was described as periods of confusion, and shot himself in the chest on 17Oct2003. Of note, the patient saw his prescribing physician on 10Jun03, and he was “doing better” with improved memory and grades. The laboratory values at the time were as follows: Trileptal = 8 (normal range 15 – 35), sodium = 140 (normal – 135 – 145), and comprehensive metabolic profile (CMP) was normal. The prescriber believed the suicide was related to Trileptal.<sup>4</sup>
- One case (ISR#3880628, Germany, 2002) of systemic lupus erythematosus (Trileptal is labeled for lupus) was reported in an 11 year old male who had received Trileptal for 5 – 6 years without incidence. At the time of diagnosis for lupus, Trileptal was discontinued without patient improvement. Trileptal was restarted and continued for a year when the patient died due to unspecified causes.
- A case (ISR#4417248, U.S., 2004) of a two day old male whose 13 week gestational exam was normal was pronounced dead. The cause of death was not specified. The mother had received multiple medications including fluoxetine, nadolol, codeine-acetaminophen, and Neurontin while pregnant.

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<sup>4</sup> DNP is currently gathering data to determine class labeling for self-injurious behavior events, including suicide.

- There was one case of hepatic failure and pneumonopathy, which was unlikely drug related.

This case (ISR#4169665, France, 2003), in a 15 year old (unknown gender) with a medical history of pulmonary aspiration, reported the patient was comatose on hospitalization from inhalation pneumonia. Subsequently, the patient developed hypoxia with a drop in blood pressure (80/30 mmHg) which likely compromised his vascular circulation with secondary effect on his liver, (major hepatic insufficiency – shock liver). Despite supportive measures, the patient died nine days after admission of hepatic failure.

- A case (ISR#3827862, Argentina, 2001) in a 10 year old female with a history of Rett’s disorder received Trileptal to treat an unspecified disorder for 1.5 years when the patient developed Nephrotic Syndrome. The patient's condition did not improve despite corticosteroid use and discontinuation of Trileptal - negative dechallenge. Her condition worsened with the development of ascites and pulmonary edema before her death 69 days after admission. The reporting physician stated this event is unlikely drug related.
- In a case (ISR#3888699, Brazil, 2002), a four year old male who was unable to swallow secondary to congenital hydrocephalus required placement of an indwelling gastric catheter. Subsequent to changing the catheter, the patient experienced intestinal perforation, infectious peritonitis, and septicemia. Post surgical repair of a fistula, the patient died. The culmination of gastric events is likely secondary to trauma regarding the catheter change, and unlikely drug related.

In conclusion, we reviewed 13 fatal cases of various events coincident with Trileptal use including seizure (1), status epilepticus (1), asphyxiation (1), cardiac arrest (1), myocarditis (1), multi-organ system failure (1), lupus erythematosus (1), unspecified (1), nephritic syndrome (1), intestinal perforation (1), hepatic failure (1), rhabdomyolysis (1), or suicide (1). There was one case of suicide that described critical subjective data. A 15 year old male with no history of psychiatric disorders or suicide attempts received Trileptal therapy and committed suicide. We could not rule out a possible association with Trileptal. Of note, cases of suicide are under review by the Division of Neurology Products and the sponsor of Trileptal. We will inform you of the findings when the information becomes available.

The remaining 12 fatal cases, although coincident with Trileptal use, involved other suspect medications and/or an underlying seizure disorder that may have contributed to and/or was secondary to the cause of death. Furthermore, some cases either lacked the clinical details necessary for a thorough evaluation or reported the cause of death as unknown.

#### 4.2.2 Non-fatal cases

##### 4.2.2.1 Non-fatal unlabeled/unexpected cases

There were 52 of 83 nonfatal cases of various events that were unlabeled/unexpected reported in association with Trileptal use. Except for events occurring in utero, most events were similar to those observed in adults. There was one compelling case of an anaphylactoid reaction that occurred 30 minutes

post first dosing with Trileptal. A complete review of anaphylactic reactions for pediatrics and adult is forthcoming in a separate DDRE review<sup>5</sup>.

The 52 cases, although coincident with Trileptal therapy, either lacked clinical details necessary for complete review, were temporally related to another drug, or were possibly confounded by multiple drug regimens and/or coexisting/underlying medical conditions. Based upon the predominant adverse event reported, the cases were classified into the following 15 categories: cardiac (1), dental (1), endocrine (8), hematologic (4), hepatobiliary (3) immunological (1), in utero (4) electrolyte (1), musculoskeletal (3), neurological (10), ophthalmic (2), psychiatric (9), renal (1), vascular (1), and general (3) events. Unlabeled events are highlighted.

#### 4.2.2.1.1 Cardiac events (n=1)

In one case (ISR# 4573299) a female initiated on April 1, 2005 Trileptal at 600 mg daily for seizure control. She experienced excessive PVCs during an electrocardiogram in April 2005. A second EKG on an unknown date showed a right bundle branch block and prolonged QT interval. A 24-hour holter monitor was considered normal with normal sinus rhythm and intermittent right bundle branch block and no premature ventricular contractions. Trileptal continued and the patient's condition was unchanged.

#### 4.2.2.1.2 Dental events (n=1)

One case (ISR# 4720249) reported the development of spotted teeth with signs of caries during the drug switch from sultiam, an antiepileptic, to Trileptal. The reporting dentist suspected a causal relationship with Trileptal.

#### 4.2.2.1.3 Endocrine events (n=8)

There were eight cases of endocrine disorders that were characterized as abnormal hormone levels (2), hypothyroidism (3), hyperthyroidism (1), hyperprolactinemia (1), and diabetes (1). The case summaries follow:

There were two closely related cases (ISR# 4944491 and 4944527) of thyroid hormone level disorders that were temporally related with symptoms. Two females (ages 14 and 15 years) received Trileptal 900 mg daily for partial seizures. The patients experienced lethargy, weight gain, mild constipation, cold intolerance, dry skin, brittle hair, irregular menses, and feeling swollen in the face. Laboratory findings revealed normal serum thyrotropin concentrations with low free thyroxine levels and a normal MRI. Treatment included levothyroxine that resolved the presenting clinical events.

In one case (ISR# 4663599) of juvenile diabetes, a 15 year old female received Trileptal 1500 mg BID for epilepsy. One month later, she was diagnosed with insulin dependent diabetes. Idiopathic juvenile onset diabetes is prevalent between the ages of 12 – 15 years,<sup>6</sup> and it is unknown what other potential factors may have contributed to this event in this case.

Five non-serious cases (ISR#s 4764540, 4738012, 4622398, 4670236, 4820524) of hormone level disorders were described as hyperprolactinemia (1), hyperthyroidism (1), and hypothyroidism (3).

#### 4.2.2.1.4 Hematologic events (n=4)

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<sup>5</sup> In AERS, we identified 10 reports of anaphylactic reactions for all ages, including one other pediatric case.

<sup>6</sup> Diabetes: Griffith's 5-minute clinical consult 14<sup>th</sup> edition (2006); electronic version.

There were four cases of blood disorders. One case (ISR# 4891056) in a 12 year old female reported ITP while receiving Trileptal for 4 years. Although her initial response to human immunoglobulin was good, her platelet levels dropped intermittently while therapy with Trileptal continued.

Another case (ISR# 4738026) reported thrombocytosis with Trileptal monotherapy of three years. Trileptal was discontinued, but no outcome was reported.

The other case (ISR# 4873101) in a three year old male who initiated Trileptal on 12/6/05 at an unknown dose for seizure control developed a fever. Amoxicillin was initiated on 12/9/05. The fevers continued and on 12/13/05, the patient developed a body rash. Trileptal and amoxicillin were discontinued on 12/15, and the patient's rash resolved. On 12/29/05, the patient developed neutropenia (ANC = 19). The patient was admitted to the hospital and the ANC progressively increased.

The last case (ISR#4763671) described mild rectal bleeding that was likely secondary to abdominal constipation and straining.

#### 4.2.2.1.5 Hepatobiliary events (n=3)

There were three cases of hepatobiliary disorders. One case (ISR# 4612814, Italy, 2005) in an 11 year old female with two suspect drugs to treat refractory seizures, phenobarbital for five years and Trileptal for 31 days, reported "severe hepatic failure." Trileptal was discontinued and the patient completely recovered.

Another hepatic failure case (ISR# 4917394) involved multiple suspect drugs with recent dose increases of phenobarbital and valproic acid. Additionally, the patient experienced chicken pox and status epilepticus. Trileptal was continued and the patient recovered.

One case of cholecystitis (ISR#4830540) described elevated liver function enzymes. After "gallbladder surgery," the levels improved.

#### 4.2.2.1.6 Immune system events (n=1)

In one case (ISR# 4958197), a 4 year old male experienced an anaphylactic reaction 30 minutes after the first dose. He experienced difficulty breathing, stridor, drooling, and croupy cough that progressed over the next three hours and required hospitalization. On admission, the patient was diagnosed with a possible anaphylactic reaction. The medical management included epinephrine, dexamethasone, and diphenhydramine. The patient recovered.

#### 4.2.2.1.7 In utero exposure (n=4)

There were four cases of adverse events occurring in utero.

One case (ISR# 4906103) reported a fetus in the first trimester exposed to multiple drugs including Trileptal. At birth, the newborn experienced a congenital anomaly described as sacrocoxitis blind fistula.

One case (ISR#4621927) of poor sucking in a newborn following use of combined Trileptal, dose titrated to 2100 mg daily, and Valium. Following delivery, the baby required placement of a nasogastric tube.

One case (ISR# 4660975) reported a neonate of 2 days old who experienced a seizure. The mother was receiving an eight drug antiepileptic regimen.

One case (ISR# 4939535) reported a newborn baby who was exposed to Trileptal in utero for two weeks before delivery, and experienced **hypotonia**.

#### 4.2.2.1.8 Electrolyte conditions (n=1)

One case (ISR# 4851713) reported mild **hyperkalemia** - 5.4 (normal 3.4 – 4.7). Because the other laboratory values (specific test(s) unspecified) were normal, the reporter suspected the blood sample hemolyzed.

#### 4.2.2.1.9 Musculoskeletal events (n=3)

Three cases of growth retardation (1), bone disorder (1), and aggravated myasthenia gravis (1). The case (ISR# 4944482) of **growth retardation** in a 10 year old male was temporally related and had a positive dechallenge. The patient received Trileptal 600 mg daily for partial seizures. He was always short in stature, but had a marked decrease in growth velocity since initiation of Trileptal. He had a normal head magnetic resonance imaging. Trileptal was discontinued and replaced with valproic acid. His growth velocity dramatically improved (9.6 cm/year) and he caught-up in his growth.

The other case (ISR# 4824801) in a 9 month old male reported concurrent Trileptal and vigabatrin, an antiepileptic, to treat epilepsy. The patient experienced pain with hip mobilization, and an X-ray revealed **epiphysiolysis** of the left femoral head. Surgery was required for repair. The drugs continued.

Another case (ISR# 4924972) reported a patient 16 years old who experience **aggravated myasthenia gravis**, and recent treatment with Keppra. It is unknown if the aggravation was due to the natural course of the disease.

#### 4.2.2.1.10 Neurologic events (n=10)

There were 10 cases of neurologic disorders. One case (ISR# 4949308, France) of a 13 month old female with an unknown genetic disorder received multiple drugs, including Trileptal. She experienced “**myoclonus** without EEG abnormality.” The dose of Trileptal was decreased and the myoclonus disappeared. Based on the lack of details in this case and in the absence of positive EEG findings, myoclonus might be related to involuntary movement and not seizure activity.

Two patients experienced **seizures** (ISR#4622454, 4687979). One was linked to a dose increase of Wellbutrin and the other did not report details or an outcome.

There were seven cases (ISR#s 4650532, 4628172, 4951773, 4701311, 4925797, 4925615, and 4910612) of **forceful eyelid closure**-1, **dystonia**-1, **depression**-1, **mental retardation**-1, **sedation**-2, and **somnolence**-1. The outcomes were non-serious in nature, and the events were explained by alternative etiology or they continued after Trileptal was discontinued (negative dechallenge). The one case of mental retardation lacked needed clinical details.

#### 4.2.2.1.11 Ophthalmic events (n=2)

There were two vision disorders associated with Trileptal. In a case (ISR# 4771943) of a nine year old male whose medical history included developmental delay, multiple medical problems, and cortical blindness since birth, he experienced oversensitive hearing, and a **decrease to visual stimulation** after a couple weeks of Trileptal.

The other case (ISR#4842195) in a 10 year old female with a history of encephalitis reported that she experienced **transient blindness** during the use of Trileptal for 7 – 10 days.

#### 4.2.2.1.12 Psychiatric events (n=9)

There were nine cases of psychiatric disorders. One case (ISR# 4909220) of a nine year old female who received Trileptal 1200 mg daily for 16 days to manage seizure activity experienced **visual hallucinations** and increased number of seizure. Trileptal was discontinued and the patient made a “complete recovery.”

One case (ISR# 4945272) reported a seven year old male who experienced **visual hallucinations** of snakes following a dose increase of Trileptal to 1500 mg and dexamethylphenidate to an unknown dose. Trileptal was discontinued and patient recovered.

One case (ISR# 4916731) of **suicidal and homicidal ideation** reported in a 14 year old male with a long history of bipolar disorder. The reporting psychiatrist stated that this was not new behavior for the patient.

**Hallucination** (ISR#4842193): A patient received multiple drugs to treat ADHD. No outcome was reported.

**ADHD** (ISR#4707224): Patient treated for unknown duration with Trileptal for epilepsy and experienced ADHD.

**Suicide** (ISR#4959795): A 15 year old female overdosed with multiple drugs including Trileptal. It is unknown if the patient was prescribed Trileptal.

**Anger, agitation, frustration, suicide attempt** (ISR#4627556): Multiple medications initiated in a patient with a history of bipolar disorder. Trileptal was discontinued and the events continued. Later, the patient attempted suicide by ingesting Trileptal tablets.

**Tantrums, aggression, and weight gain** (ISR#4775675): Trileptal that was later discontinued was used concomitantly with Adderall. No outcome was reported.

**Breath holding** (ISR# 4704878): A 14 year old boy with severe learning disabilities would hold his breath until he felt faint.

#### 4.2.2.1.13 Renal events (n=1)

In one case (ISR# 4939536) a 10 year old female presented with **hematuria** that was related to IgA nephropathy, which was supported with medical intervention. Trileptal therapy continued. The patient recovered.

#### 4.2.2.1.14 Vascular events (n=1)

One case (ISR# 4648682) in a 12 year old male reported Trileptal 750 mg daily for seizure. The patient experienced “**rheumatic purpura**” that resolved with rest and medication. Trileptal continued, and no outcome was reported. Because Henoch-schonlein purpura is prevalent in children, other unknown etiologies remain suspect, including insect bites.

#### 4.2.2.1.15 General events (n=3)

One case (ISR# 4903686) of rash, conjunctivitis, and bladder retention was reported in a three year old male during the use of Trileptal.

One case (ISR# 4652284) of edema in the face, hands, and feet occurred during Trileptal use. Nephrotic syndrome was ruled out. The reporting nephrologist suspected causality was related to hereditary protein loss.

One case (ISR #4687977) in a 4 year old male who was hospitalized for decreased oxygen saturation after receiving Trileptal for six weeks. No outcome was reported.

#### 4.2.2.2 Non-fatal labeled/expected cases

Of the 84 nonfatal cases, 31 cases of various events associated with Trileptal are listed or implied in the current product label. The status in labeling for the various adverse events included Warnings for serious skin reactions (including SJS) – 7, and hyponatremia -1, Precautions for multiple organ system hypersensitivity – 2, and Other Adverse Events observed during postmarketing included aggravated seizure – 4, hyperglycemia – 3, aggressive reaction – 2, increased levels of transaminases – 2, ataxia – 1, constipation – 1, facial edema -1, gingival bleeding – 1, hives – 1, leukopenia – 1, muscle spasm – 1, priapism – 1, thrombocytopenia – 1, and vomiting – 1. There were not enough compelling cases of any one event to warrant more prominent exposure in the label.

### 5.0 Conclusion

We reviewed 84 cases of various adverse events reported in association with Trileptal during the pediatric exclusivity period in children under the age of 17 years, including one fatal case. Collectively, we reviewed 13 pediatric death cases including 12 cases outside the pediatric exclusivity period and one case during the pediatric exclusivity period.

Of the 13 fatal cases, one case of suicide occurred in a 15 year old male with no known history of psychiatric disorders or prior suicide attempts. After receiving Trileptal for eight months, the patient shot himself in the chest. Of note, cases of suicide are under review by the Division of Neurology Products and the sponsor for Trileptal. We will inform you of the findings when the information becomes available. The remaining 12 death cases were equivocally related to Trileptal and include the one fatal case reported during the pediatric exclusivity period. This case (from China, 2005) involved a six year old who “died due to rhabdomyolysis” (CPK = 100,000 units unspecified). The case contained sparse information and did not provide adequate details to assess.

The remaining 83 nonfatal cases reported during the pediatric exclusivity period were stratified into adverse events that were unlabeled/unexpected (52), or labeled/expected (31). The 53 unlabeled events included one case of an anaphylactic reaction occurring 30 minutes post first dose of Trileptal in a four year old male. A full evaluation of similar AERS reports involving all age groups is forthcoming in a separate DDRE review. The other 52 unlabeled cases involved too few cases to characterize any one adverse event as a potential safety signal. Although the events occurred in pediatric patients, the described events were similar to those observed in adults, except for events that occurred in utero. Of 31 labeled events, there were not enough cases of any one event to warrant more prominent placement of the event in

the current label. For all events, we will continue routine postmarketing monitoring. Please contact me at #60153 if further information is needed.

## **Appendix I: Pediatric Dosing**

### Adjunctive Therapy (aged 2 – 16 years)

Treatment should be initiated at a daily dose of 8-10 mg/kg generally not to exceed 600 mg/day, given in a BID regimen. The target maintenance dose of Trileptal should be achieved over two weeks, and is dependent upon patient weight, according to the following chart:

20-29 kg - 900 mg/day

29.1-39 kg - 1200 mg/day

>39 kg - 1800 mg/day

In the clinical trial, in which the intention was to reach these target doses, the median daily dose was 31 mg/kg with a range of 6-51 mg/kg.

In pediatric patients aged 2 - <4 years, treatment should also be initiated at a daily dose of 8-10 mg/kg generally not to exceed 600 mg/day, given in a BID regimen. For patients less than 20 kg, a starting dose of 16-20 mg/kg may be considered. The maximum maintenance dose of Trileptal should be achieved over 2-4 weeks and should not exceed 60 mg/kg/day in a BID regimen.

In clinical trial in pediatric patients (2 to 4 years of age) in which the intention was to reach the target dose of 60 mg/kg/day, 50% of patients reached a final dose of at least 55 mg/kg/day.

Under adjunctive therapy (with and without enzyme-inducing AEDs), when normalized by body weight, apparent clearance (L/hr/kg) decreased when age increased such that children 2 <4 years of age may require up to twice the oxcarbazepine dose per body weight compared to adults; and children 4 to ≤ 12 years of age may require a 50% higher oxcarbazepine dose per body weight compared to adults.

### Conversion to Monotherapy (aged 4-16 years)

Patients receiving concomitant antiepileptic drugs may be converted to monotherapy by initiating treatment with Trileptal at approximately 8-10 mg/kg/day given in a BID regimen, while simultaneously initiating the reduction of the dose of the concomitant antiepileptic drugs. The concomitant antiepileptic drugs can be completely withdrawn over 3-6 weeks while Trileptal may be increased as clinically indicated by a maximum increment of 10 mg/kg/day at approximately weekly intervals to achieve the recommended daily dose. Patients should be observed closely during this transition phase.

The recommended total daily dose of Trileptal is shown in the table below.

### Initiation of Monotherapy

Patients not currently being treated with antiepileptic drugs may have monotherapy initiated with Trileptal. In these patients, Trileptal should be initiated at a dose of 8-10 mg/kg/day given in a BID regimen. The dose should be increased by 5 mg/kg/day every third day to the recommended daily dose shown in the table below.

Table 7  
 Range of Maintenance Doses of Trileptal® for  
 Children by Weight During Monotherapy

Weight in kg	From	To
	Dose (mg/day)	Dose (mg/day)
20	600	900
25	900	1200
30	900	1200
35	900	1500
40	900	1500
45	1200	1500
50	1200	1800
55	1200	1800
60	1200	2100
65	1200	2100
70	1500	2100

## **Appendix II: Limitations of AERS**

### **Limitations of the Adverse Event Reporting System (AERS)**

The voluntary or spontaneous reporting of adverse events from health care professionals and consumers in the U.S reflects underreporting and also duplicate reporting. For any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s). The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues. Therefore, counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing drug risk between drugs.

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/s/

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