Pediatric Focused Safety Review: Sabril® (vigabatrin) Pediatric Advisory Committee Meeting April 12, 2016

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Outline

- Background Information
- Relevant Labeling
- Drug Use Trends
- Safety
- Summary

Background Drug Information
Sabril® (vigabatrin)

- **Drug:** Sabril®
- **Formulations:**
  - 500 mg tablets for oral use
  - 500 mg powder for oral solution
- **Sponsor:** Lundbeck LLC
- **Original Market Approval:** August 21, 2009
- **Pediatric Labeling Changes:** October 26, 2013 (initiated PAC review)
- **Therapeutic Category:** Antiepileptic
- **Postmarketing Requirements:** Registry to further explore visual loss (Study submission due date: September 2016).

Background Drug Information
Sabril® (vigabatrin)

- **Indications:**
  - Use as adjunctive treatment patients 10 years of age and older with refractory complex partial seizures (CPS) that have responded inadequately to several alternative treatments
  - Monotherapy in infants 1 month to 2 years of age with infantile spasms

Pediatric Studies*
Sabril® (vigabatrin)

Pediatric Written Request:

- Issued on August 25, 2011 and amended on April 18, 2013.
- Vigabatrin was studied for the adjunctive treatment of uncontrolled CPS in three double-blind placebo controlled studies enrolling a total of 373 patients. The results of the studies were pooled and used in a pharmacokinetic (PK) bridging analysis defining a weight-normalized dose-response, and showing that a similar dose-response relationship exists between pediatric patients and adult patients to establish efficacy and dosing in pediatric patients 10 to 16 years of age.
- Duration of therapy for infantile spasms was evaluated in a post hoc analysis of a Canadian Pediatric Epilepsy Network (CPEN) study. The 38/68 infants in the study who had responded to vigabatrin therapy (complete cessation of spasms and hypsarrhythmia) continued vigabatrin therapy for a total duration of 6 months. The 38 infants who responded were then followed for an additional 18 months after discontinuation of vigabatrin to determine their clinical outcome. A post hoc analysis indicated no observed recurrence of infantile spasms in any of these 38 infants.
- Exclusivity was granted on October 3, 2013.
- Studies in CPS also fulfilled requirements under the Pediatric Research and Equity Act (PREA).

*Study and labeling change which triggered the current PAC review

Relevant Labeling, continued
Sabril® (vigabatrin)*

WARNING: VISION LOSS

- **SABRIL causes progressive and permanent bilateral concentric visual field constriction in a high percentage of patients. In some cases, SABRIL may also reduce visual acuity.**
- **Risk increases with total dose and duration of use, but no exposure to SABRIL is known that is free of risk of vision loss.**
- **Risk of new and worsening vision loss continues as long as SABRIL is used, and possibly after discontinuing SABRIL.**
- **Unless a patient is formally exempted, periodic vision assessment is required for patients on SABRIL. However, this assessment cannot always prevent vision damage.**
- **SABRIL can cause permanent vision loss. SABRIL is available only through a restricted program called the SHARE Program.**

*Box warning from highlights; body of labeling contains expanded box warning for vision loss

Relevant Labeling, continued
Sabril® (vigabatrin)

2 DOSAGE AND ADMINISTRATION

Indication	Initial Dose	Maintenance Dose
Refractory Complex Partial Seizures* 10 to 16 years of age	≤ 60 kg: 250 mg twice a day > 60 kg: 500 mg twice a day	≤ 60 kg: 1000 mg twice a day > 60 kg: 1500 mg twice a day
Infantile Spasms 1 month to 2 years of age	25 mg/kg twice a day	75 mg/kg twice a day

* and have responded inadequately to several alternative treatments

Relevant Labeling, continued
Sabril® (vigabatrin)

5 WARNINGS AND PRECAUTIONS

5.1 Vision Loss

5.2 SABRIL SHARE Program

5.3 Magnetic Resonance Imaging (MRI) Abnormalities in Infants

5.4 Neurotoxicity

5.5 Suicidal Behavior and Ideation

5.6 Withdrawal of Antiepileptic Drugs (AEDs)

5.7 Anemia

5.8 Somnolence and Fatigue

5.9 Peripheral Neuropathy

5.10 Weight Gain

5.11 Edema

Relevant Labeling, continued
Sabril® (vigabatrin)

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

Safety and effectiveness of SABRIL as adjunctive treatment of refractory complex partial seizures in pediatric patients aged 10 to 16 years of age have been established. The safety and effectiveness of SABRIL have not been established in pediatric patients under 10 years of age with refractory complex partial seizures.

The safety and effectiveness of SABRIL as monotherapy for pediatric patients with infantile spasms (1 month to 2 years of age) have been established.

Abnormal MRI signal changes were observed in infants.

Post hoc analysis of the Canadian Pediatric Epilepsy Network (CPEN) suggests that a total duration of 6 months of vigabatrin therapy is adequate for the treatment of infantile spasms.

Relevant Labeling, continued
Sabril® (vigabatrin)

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics (PK)

PK data supports dosing pediatric patients infants 1 month to 2 years of age with infantile spasms and 10 years of age and older with PCS

14 CLINICAL STUDIES

Clinical study data for pediatric patients 1 month to 2 years of age with infantile spasms and PCS 10 years of age and older to support use

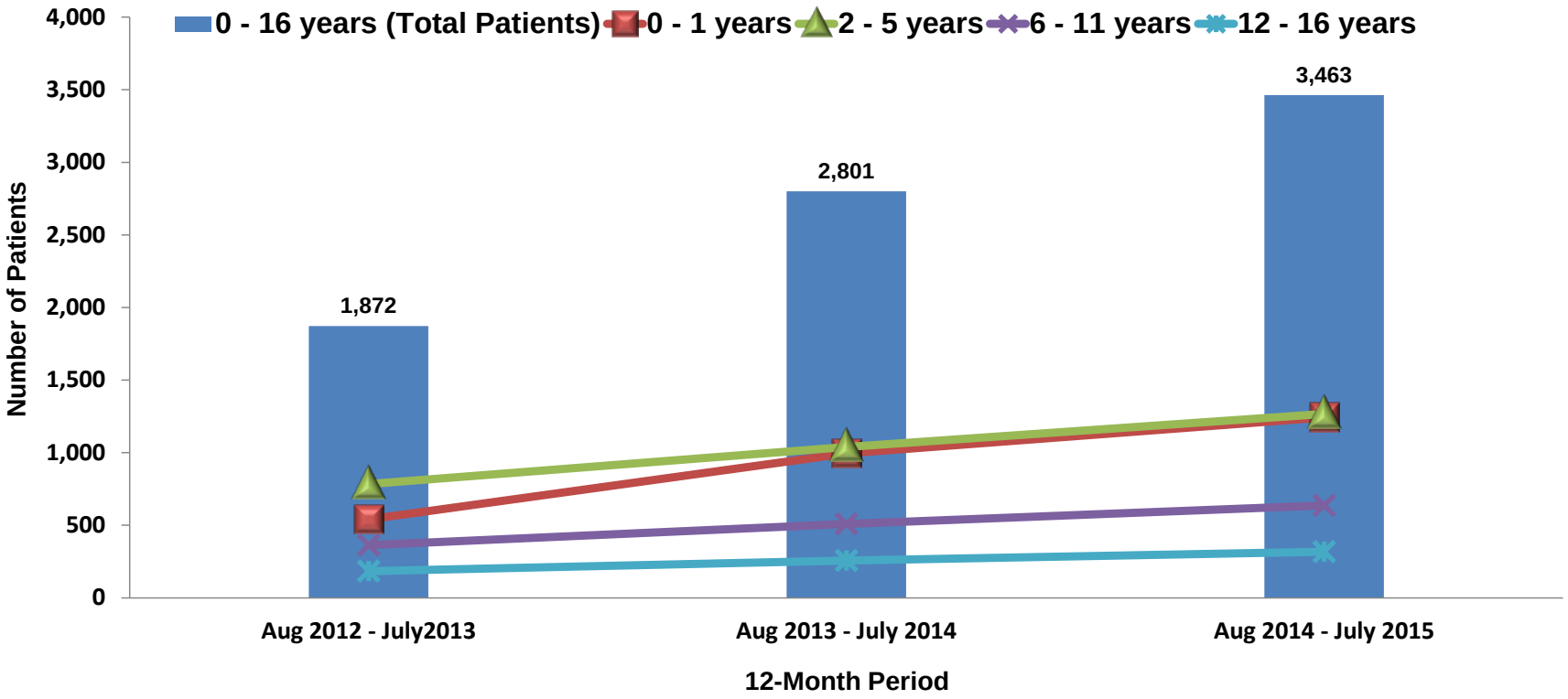
Drug Utilization Data: Sabril ® (vigabatrin)

Nationally Estimated Number of Patients with a Dispensed Prescription for Sabril (vigabatrin) Stratified by Patient Age, from U.S. Mail Order Pharmacies August 1, 2014 - July 31, 2015		
	Patients (N)	Share (%)
Total Patients	**4,279**	**100.0%**
0 - 16 years	**3,463**	**80.9%**
0 - 1 years	1,242	35.9%
2 - 5 years	1,266	36.6%
6 - 11 years	636	18.4%
12 - 16 years	318	9.2%
17 -64 years	**787**	**18.4%**
65+ years	**29**	**0.7%**

Source: Symphony Health Solutions' PHAST Patient Monthly. August 2014 – July 2015. Extracted September 2015.

Drug Utilization Data: Sabril ® (vigabatrin)

Nationally Estimated Number of Pediatric Patients (0-16) with a Dispensed Prescription for Vigabatrin from US Mail Order Pharmacies



Source: Symphony Health Solutions' PHAST Patient Monthly. August 2012 – July 2015. Extracted Sept-2015.

Sabril ® (vigabatrin) Utilization Data

Prescribing Specialty[1] and Diagnosis[2]
August 2012 – July 2015, Aggregate

- **Top Prescribing Specialties**
  (% of total mail order prescriptions dispensed)
  - Neurology (77% of total prescriptions)
  - **Pediatrics (9% of total prescriptions)**

- **No diagnosis** data associated with use of vigabatrin in pediatric patients aged 0-16 years were captured in the U.S. office-based physician survey database

[1]IMS, National Prescription Audit (NPA). August 2012 – July 2015. Extracted October 2015
[2]Encuity Research, LLC.,Treatment Answers™ Audit. August 2012 – July 2015. Extracted October 2015.

Total Number of FAERS Reports: Sabril® (vigabatrin)* August 1, 2013 to July 31, 2015

	All reports (US)	Serious† (US)	Deaths (US)
Adults (≥ 17 years)	429 (409)	283 (263)	35 (35)
Pediatrics (0 to < 17 years)	1305 (1243)	903 (847)	165 (158)**

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

† Serious adverse drug experience per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.

** 50 additional cases of pediatric deaths were identified among cases not reporting an age

Selection of Pediatric FAERS Cases: Sabril® (vigabatrin)

- August 1, 2013 to July 31, 2015
  - Deaths (n=154, after excluding 4 duplicate reports)
- August 21, 2009 to July 31, 2015
  - Events of Special interest (n=68)
    - Blindness (unlabeled, n=28)
    - Abnormal MRI (labeled, n=27)
    - Renal Events (unlabeled, n=8)
    - Pancreatitis (unlabeled, n=5)

Characteristics of Pediatric Death Cases by Reported Reason for Use: Sabril® (vigabatrin) (N=145*)

Reason for use		Infantile Spasms (n=121)	Seizures/Epilepsy (n=24)
Age N=145	≤ 2 years 3-10 years > 10 years	66 51 4	7 12 5
Sex n=141	Male Female	62 55	11 13
Total Daily Dose (mg)† n=141	Range Median Mean	300-6000 1000 1264	450-4500 2000 2002
Dosing Frequency per day N=141	Once Twice Three times Four times	11 101 6 0	6 14 2 1
Time to Death‡ n=99	Range Median Mean	2 days-5.9 years 1 year 1.5 years	1 day-7.9 years 2.1 years 2.4 years

***** Reported information extracted from the narrative field; 2 patients with tuberous sclerosis not included

† Recommended dose in infantile spasms patients (1 month-2 years of age): 25mg/kg twice daily (maximum 75mg/kg twice daily); in CPS patients (10-16 years of age): (25-60kg): 250mg twice daily (maximum 1000mg twice daily) and (> 60kg): 1500mg twice daily

‡ Should be withdrawn if it fails to show substantial clinical benefit within 2-4 weeks in infantile spasms patients and within 3 months in CPS patients

Characteristics of All Pediatric Death Cases: Sabril® (vigabatrin) (N=154**)

Age* n=154	0 – < 1 month 1 month - < 2 years 2- < 6 years 6- <12 years 12- < 17 years	1 69 61 17 6
Sex n=150	Male Female	79 71
Total Daily Dose (mg) n=146	Range Median Mean	150-6000 1200 1438
Reason for Use n=147	Infantile spasms Partial seizures Generalized seizure Seizures epilepsy NOS Tuberous sclerosis	121 11 4 9 2

*Report extracted from the narrative field
**Four duplicate reports excluded

Characteristics of All Pediatric Death Cases: Sabril® (vigabatrin) (N=154), Continued

Time to Death† n=100	Range Median Mean	1 day to 7.9 years 1.1 years 1.7 years
Cause of Death (System Organ Class)	Unknown Respiratory, Thoracic and Mediastinal Disorders‡ Cardiac Disorders§ Nervous System Disorders‖ General Disorders/Administration Site Conditions¶ Infections and Infestations** Surgical and Medical Procedures†† Vascular Disorders‡‡	106 24 10 10 1 1 1 11

* Reported information extracted from the narrative field
† Time from the initial drug exposure to death (approximates duration of therapy)
‡ Respiratory failure, respiratory distress, respiratory issues, aspiration pneumonia
§ Cardiac arrest, cardio-respiratory arrest, heart failure
‖ Encephalopathy, seizures/epilepsy, neurological disease, underlying brain malformation
¶ Natural causes
** Sepsis
†† Withdrawal of life support
‡‡ Circulatory collapse

Characteristics of Pediatric Death Cases: Sabril® (vigabatrin) (n=154)

- Cause of death was unknown or not reported in 106 (69%) cases.
- When reported, causes of death included respiratory in 24 (16%), cardiac in 10 (6%), and neurological 10 (6%) events consistent with the natural history and poor prognosis of the disorders.
- Clinical details surrounding death were not well-described or contained insufficient information to assess causality in a population with other comorbid disorders.
- Most cases described disease progression, infection, respiratory insufficiency and underlying congenital disorders such as Aicardi's, Cockayne, Dandy-Walker, Miller-Diecker, Ohtahara, and Leigh syndrome as possible contributory factors.
- In cases where the weight was reported, vigabatrin was dosed appropriately.

Selection of Pediatric FAERS Cases: Sabril® (vigabatrin)

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    - Renal Events (unlabeled, n=8)
    - Pancreatitis (unlabeled, n=5)

Events of Special Interest: Blindness (n=28), Sabril® (vigabatrin)

- Blindness was reviewed as a possible event of higher severity than vision loss, a labeled event.
- Reported use: infantile spasms (n=14), seizures/epilepsy NOS (n=3), partial seizures (n=1), and encephalopathy (n=1)
- Age: 4 months to 14 years (mean 3.7 years, median 2 years)
- Daily dose: 150 mg to 3000 mg (mean 1400 mg, median 1500 mg)
- 18 cases had insufficient information to assess the event, and in 2 cases blindness preceded vigabatrin exposure.
- 8 cases are described on the next slide.

Events of Special Interest: Blindness (n=28), Sabril® (vigabatrin), continued

- 8 cases with adequate details for review reported progression of visual loss.
  - Visual changes in these 8 cases were consistent with the labeling information (retinal toxicity; visual field loss).
  - Time to event: 9 months to 4 years
  - Vigabatrin was stopped in 4 patients, and continued in 4 patients
- Comorbid conditions such as premature birth, chromosomal disorders, tuberous sclerosis, infantile spasms, brain injury with developmental disorder and cerebral palsy, or concomitant medications may have affected the association.
- The role of vigabatrin in these 8 cases could not be ruled out.

Events of Special Interest: Abnormal MRI (n=27), Sabril® (vigabatrin)

- Age: 4 months to 6 years (mean 1.5 years, median 1 year)
- Daily dose: 750 mg to 2400 mg (mean 1300 mg, median 1000 mg)
- 12 cases had insufficient details for assessment.
- 6 cases reported abnormal MRIs but follow-up MRI and event outcome were not reported.
- 4 cases from literature reported MRI signal changes coincident with West Syndrome.
  - 3 cases (ages 3, 4 and 6 months) exposed to vigabatrin experienced MRI changes after 3, 5 and 16 months, respectively.
  - 1 case (age 4 months) experienced MRI changes prior to vigabatrin exposure.

Events of Special Interest: Abnormal MRI (n=27), Sabril® (vigabatrin), continued

- 5 cases reported coincident movement disorders and positive dechallenge after vigabatrin discontinuation.
  - 3 cases reported normalization in MRI signal changes and movement disorder after vigabatrin discontinuation.
  - 2 cases reported improved MRI signal changes after vigabatrin discontinuation.
- MRI signal changes, when reported (such as increased T2 signal or restricted basal ganglia, brainstem or thalami diffusion) were consistent with vigabatrin labeling.

Events of Special Interest: Renal Events (n=8), Sabril® (vigabatrin)

- Events of renal disorder (n=4), renal failure (n=3), or renal impairment (n=1) were reported
- Ages: 7 months to 8.7 years (mean 3.9 years, median 2.5 years)
- Daily dose: 124 mg to 2000 mg (mean 1050 mg, median 1000 mg)
- 3 cases had insufficient information for clinical assessment.
- 5 cases of multi-system organ failure, nephrolithiasis, stage 4 chronic kidney disease, Leigh Syndrome and Chiari type 1 malformation may have affected causality.
- The role of vigabatrin renal impairment in these 5 cases could not be ruled out.

Events of Special Interest: Pancreatitis (n=5), Sabril® (vigabatrin)

- Age: 2.4 years to 12 years (mean 4.9 years, median 3.6 years)
- Daily dose: 500 mg to 1600 mg (mean 1160 mg, median 1200 mg)
- 2 cases did not include sufficient information for assessment.
- 2 cases reported being on a ketogenic diet; stopping the diet and vigabatrin resulted in resolution in one case, stopping the diet alone resulted in resolution in the second case.
- 1 case resolved despite continued vigabatrin.
- Concomitant medications included levetiracetam (n=3) and topiramate (n=1), both labeled for pancreatitis, and rufinamide (n=1), phenobarbital (n=1), and clobazam (n=1), unlabeled for pancreatitis.

Summary of Safety Reviews Sabril® (vigabatrin)

- This concludes the pediatric focused safety review of FAERS reports.
- Case reports with an outcome of death described disease progression in a population with underlying disorders and conditions having a poor prognosis and could be expected. Vigabatrin was not determined to be a causative factor.
- Cases of visual loss and MRI changes in infants are consistent with the warnings and precautions in labeling.
- No new safety signals were identified.
- FDA recommends continued routine monitoring.
- Does the committee concur?

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