Sabril® (vigabatrin) Tablets for Refractory Complex Partial Seizures

United States Food and Drug Administration
Peripheral and Central Nervous System Drugs Advisory Committee
January 7, 2009
Sabril® (vigabatrin) Tablets for Refractory Complex Partial Seizures

Introduction

Tim Cunniff, PharmD
Vice President
Global Regulatory Affairs, Pharmacovigilance & Clinical Quality Assurance
Ovation Pharmaceuticals, Inc.
Proposed Indication

NDA 20-427 (500 mg tablet)

- Sabril is indicated as adjunctive therapy for adult patients with refractory complex partial seizures (CPS) who have inadequately responded to alternative treatments and for whom the potential benefits outweigh the potential risk of developing the peripheral visual field defect (pVFD). **Sabril is not indicated as a first-line agent for CPS.**
Worldwide Status

- Vigabatrin (VGB) currently available in more than 50 countries
  - North America: Canada, Mexico
  - Europe: Most countries within the EU
  - ROW: Many countries in Asia, Latin America, Africa/Middle East

- More than 1.5 million patients have received VGB over the past 19+ years
Vigabatrin Worldwide and US Development History

**Worldwide**

- **1975**: VGB first synthesized
- **1979**: Clinical trials begin in Europe
- **1980**: Clinical trials begin in US
- **1983**: Partial IND clinical hold due to IME in animals
- **1989**: 1st marketing approval in UK
- **1990**: Resolution of partial IND clinical hold

**US**

- **1979**: Clinical trials begin in Europe
- **1980**: Partial IND clinical hold due to IME in animals
- **1989**: 1st marketing approval in UK
- **1990**: Resolution of partial IND clinical hold
Vigabatrin Worldwide and US Development History

**Worldwide**

- **1994**: CPS NDA submitted by prior sponsor
- **1997**: 1st reports of pVFD in Europe
- **1999**: EMEA: benefit/risk profile positive, Article 12 studies requested
- **2007**: Last Article 12 study submitted

**US**

- **1994**: CPS NDA submitted by prior sponsor
- **1997**: “Approvable” letter for CPS
- **1998**: “Non-approvable” letter for CPS
- **2004**: Ovation-NA rights
- **2006**: Reports of MRI abnormalities in IS
- **2008**: CPS amendment and IS NDA accepted
CPS—Key Considerations (1)

- Refractory CPS: Serious and life-threatening disease with unmet medical need
- Efficacy of VGB for CPS well established
  - Pivotal US clinical studies (025 and 024) meet FDA’s statutory definition of adequate and well controlled
  - Therapeutic response observed within 4 - 6 weeks
- Safety of VGB is well characterized
  - > 4000 patients exposed to VGB in > 100 clinical trials
  - > 1.5 million patients have received VGB over past 19+ years
Many essential features of pVFD now better understood
- Estimated prevalence in adults with refractory CPS is 25% (range of 17% - 92% reported in the literature)
- Typically occurs after prolonged VGB use, although there are infrequent reports prior to 6 months of VGB exposure
- Most often mild or moderate, rarely severe
- Appears to progress slowly while on drug
- Irreversible if it occurs
- Can be detected by age-appropriate ophthalmologic monitoring before becoming clinically meaningful
CPS—Key Considerations (3)

- Risk Evaluation and Mitigation (REMS) Plan
  - Labeling
    - Package Insert with prominent pVFD Black Box Warning
    - Patient Medication Guide
  - Communication Plan/Education Programs to reinforce key risk messages
  - Elements to Assure Safe Use
    - Restriction of initial prescription to board-certified neurologists
    - Restriction of dispensing to select specialty pharmacies (controlled distribution)
    - Enforced benefit/risk assessment after initial evaluation phase
    - Enforced ophthalmologic monitoring
    - Sabril registry
# Today’s Agenda

<table>
<thead>
<tr>
<th>Topic</th>
<th>Presenter</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unmet Medical Need</td>
<td>R. Edward Faught, MD</td>
<td>University of Alabama School of Medicine University of Alabama at Birmingham</td>
</tr>
<tr>
<td>Efficacy and General Safety</td>
<td>Christopher Silber, MD</td>
<td>Ovation Pharmaceuticals, Inc.</td>
</tr>
<tr>
<td>Peripheral Visual Field Defect Assessment</td>
<td>Robert C. Sergott, MD</td>
<td>Wills Eye Institute Thomas Jefferson University, Philadelphia</td>
</tr>
<tr>
<td>Monitoring</td>
<td></td>
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</tr>
<tr>
<td>Peripheral Visual Field Defect Characteristics</td>
<td>Stephen M. Sagar, MD</td>
<td>Ovation Pharmaceuticals, Inc.</td>
</tr>
<tr>
<td>Risk Evaluation and Mitigation Strategy</td>
<td>Tim Cunniff, PharmD</td>
<td>Ovation Pharmaceuticals, Inc.</td>
</tr>
<tr>
<td>Benefit/Risk Assessment</td>
<td>Roger J. Porter, MD</td>
<td>University of Pennsylvania, Philadelphia Uniformed Services University of the Health Sciences, Bethesda</td>
</tr>
</tbody>
</table>
Consultants

- Richard M. Bittman, PhD
  Bittman Biostat, Inc.

- D. Reid Patterson, DVM, PhD
  Reid Patterson Consulting, Inc.

- Carol Westall, PhD
  University of Toronto Hospital for Sick Children

- James W. Wheless, MD
  The University of Tennessee Health Science Center
Sabril® (vigabatrin) Tablets for Refractory Complex Partial Seizures
An Unmet Need for Therapies

R. Edward Faught, MD
Professor and Vice Chair, Department of Neurology
University of Alabama School of Medicine
University of Alabama at Birmingham
Director, UAB Epilepsy Center
Seizures and Epilepsy

- **Seizure**: A brief, abnormal brain electrical discharge causing a change in behavior
- **Epilepsy**: A tendency to have repeated seizures
- **Prevalence of epilepsy**: 1% to 2% of population\textsuperscript{a,b}
- **Causes of epilepsy**
  - Genetic
  - Biochemical
  - Traumatic
  - Neoplastic
  - Vascular
  - Degenerative
- **The cause is unknown in 50% of patients**

Classification of Epileptic Seizures

What Is a Complex Partial Seizure?

- Blank, unresponsive stare, often 1 to 2 minutes
- Automatisms: meaningless repetitive speech or movements
- Frequency varies widely: daily to monthly
- May progress to tonic-clonic convulsions in 50% of patients
- Period of confusion for minutes to hours after each seizure
Impact of Refractory Epilepsy on Quality of Life (N = 503)

- Caring for your children: 12%
- Handling household details: 20%
- Doing household chores: 19%
- Exercising: 24%
- Traveling vacations > 1 week: 26%
- Enjoying leisure activities: 20%
- Participating in social activities: 21%
- Driving: 47%
- Holding part-time job: 36%
- Holding full-time job: 40%

Percentage of patients reporting problems

Uncontrolled Epilepsy May Be Fatal

Seizure Treatment Is Often Unsatisfactory

- 36% of patients with epilepsy are refractory, defined as having failed 2 monotherapies and at least one drug combination\(^a\)
- In clinical trials for patients with refractory seizures\(^b\)
  - Only 20% to 50% achieved a 50% reduction in seizure frequency
  - Fewer than 10% became seizure-free

What is “Refractory” Epilepsy?

- Failure of $\geq 2$ drugs and $\geq 1$ drug combination
  - Indicates $< 20\%$ chance of control with any current drug\textsuperscript{a,b}

- Best defined by numbers of drugs tried at adequate dosages without complete seizure control

- Not defined by either frequency or severity of seizures

What Are the Treatment Options for Patients With Refractory Complex Partial Seizures?

- Polytherapy combinations, 2 to 4 drugs
- Vagal nerve stimulator implantation
- Brain surgery to remove the seizure focus
- Less commonly used drugs with greater side-effect potentials
There are multiple fundamental etiologies of epilepsy.

To address these varied etiologies, antiepileptic drugs differ in their mechanisms of actions.

Physicians cannot predict the most effective drug for a specific patient for refractory patients; several different drugs and combinations are often tried.

Every time a new drug becomes available, some refractory patients become seizure-free.

Is It Worthwhile to Keep Trying New Therapies in Refractory Epilepsy?

…no matter how many AED therapies have failed, there is always hope of a meaningful clinical remission in this population.


Figure modified with permission from: Schiller Y and Najjar Y. Neurology. 2008;70:54-65.
Varied Mechanisms of Action of Antiseizure Drugs

- Sodium channel blockers
  - Phenytoin, carbamazepine, lamotrigine
- Postsynaptic GABA receptor facilitators
  - Benzodiazepines, barbiturates
- Modulators of neurotransmitter release
  - Levetiracetam, gabapentin, pregabalin
- Mixed actions
  - Valproate, topiramate, zonisamide, felbamate
- GABA metabolic blocker
  - Vigabatrin
## Potentially Serious or Fatal Side Effects of Current Antiseizure Drugs

<table>
<thead>
<tr>
<th>Phenytoin</th>
<th>Carbamazepine</th>
<th>Sodium valproate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>Rash</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Pseudolymphoma</td>
<td>Bone marrow suppression</td>
<td>Hepatic failure</td>
</tr>
<tr>
<td>Lupus syndrome</td>
<td>Cardiac dysrhythmia</td>
<td>Hyperammononemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FBM</th>
<th>LTG</th>
<th>TGB</th>
<th>TPM</th>
<th>ZNS</th>
<th>LEV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aplastic anemia</td>
<td>Rash</td>
<td>Rash</td>
<td>Metabolic acidosis</td>
<td>Rash</td>
<td>Depression</td>
</tr>
<tr>
<td>Hepatic failure</td>
<td>Multi-organ failure</td>
<td>Nonconvulsive status epilepticus</td>
<td>Cognitive slowing</td>
<td>Fever</td>
<td>Hostility</td>
</tr>
</tbody>
</table>
Felbamate—An Example of a Drug for Refractory Epilepsy

- 1993: FDA approved
- 1994: Discovery of ~ 1 in 5000 chance of liver failure or aplastic anemia; 1 in 10,000 chance of fatal outcome
  - FDA allowed continued use with more restrictive labeling
- Risk/benefit ratio still considered favorable for some patients with hard-to-control seizures: estimated 35,000 new patient starts 1996 - 2006
- Illustrates the usefulness of a specific drug for a small but critical segment of patients

A Potential Vigabatrin Candidate

A 35-yr-old woman had head trauma from an auto accident at age 22 then began to have staring spells lasting 2 minutes at age 23. At age 25, she had a convulsion. Phenytoin and carbamazepine therapies caused rash; topiramate caused confusion. Vagal nerve stimulation was ineffective. Oxcarbazepine reduced seizure frequency from 5/month to 2/month, but she eventually lost her job as a bank teller.

Evaluation for surgery included an MRI (normal) and a video-EEG (bilateral independent temporal lobe seizures onsets). Therefore surgery was not considered an option. Additional drug trials are planned.
Summary

- Refractory epilepsy is common, degrades quality of life, is dangerous, and may be fatal
- Complex partial seizures are often poorly controlled by current therapies
- Favorable drug response is unpredictable
- We need a wide variety of choices of drugs, especially those with different mechanisms of action and different side-effect profiles
Sabril® (vigabatrin) Tablets for Refractory Complex Partial Seizures: Efficacy and General Safety

Christopher Silber, MD
Vice President, Clinical Affairs
Ovation Pharmaceuticals, Inc.
Overview

- Clinical pharmacology
- Clinical development program
  - Efficacy in refractory complex partial seizures (CPS)
  - Safety
Summary of VGB in Refractory CPS

- Efficacy well established
- Rapid onset—within 4 to 6 weeks
- 2 pivotal studies meet FDA regulatory requirements for efficacy
- Safety profile well characterized
- Additional safety concerns
  - MRI abnormalities
  - Peripheral visual field defect (pVFD)
Vigabatrin—Unique Mechanism of Action

GABA is an inhibitory neurotransmitter

VGB selectively and irreversibly inhibits GABA-T (prevents breakdown of GABA molecules)

- Increases number of GABA molecules
- Decreases seizure activity

GABA-T = GABA-transaminase; SSA = Succinic semialdehyde.
Clinical Pharmacology Overview

- Orally absorbed, linear PK
- No clinically relevant effect of
  - Food, gender, race
- No clinically relevant drug-drug interactions
- Age-related $t_{1/2}$
  - Infants = 5.65 hr
  - Adults = 7.5 hr
- VGB plasma levels do not correlate with clinical effect
Overview

- Clinical pharmacology
- Clinical development program
  - Efficacy in refractory complex partial seizures (CPS)
  - Safety
Study Design—Adjunctive Therapy for Refractory CPS
Studies 025 and 024

**Baseline period**
- 8 weeks

**Titration period**
- 6 weeks

**Maintenance period**
- 12 weeks

**Study 025 (N = 174)**
- Placebo (n = 45)
- VGB 1 g/day (n = 45)
- VGB 3 g/day (n = 41)
- VGB 6 g/day (n = 43)

**Study 024 (N = 182)**
- Placebo (n = 90)
- VGB 3 g/day (n = 92)
### Refractory Patient Population

**Studies 025 and 024**

<table>
<thead>
<tr>
<th>Patients with prior AED(^a) usage, %</th>
<th>Study 025 N = 174</th>
<th>Study 024 N = 182</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\geq 1) AED</td>
<td>93.1</td>
<td>100.0</td>
</tr>
<tr>
<td>(\geq 2) AEDs</td>
<td>87.9</td>
<td>96.7</td>
</tr>
<tr>
<td>(\geq 3) AEDs</td>
<td>74.7</td>
<td>80.8</td>
</tr>
<tr>
<td>(\geq 4) AEDs</td>
<td>48.3</td>
<td>51.6</td>
</tr>
<tr>
<td>(\geq 5) AEDs</td>
<td>19.5</td>
<td>14.8</td>
</tr>
<tr>
<td>(\geq 6) AEDs</td>
<td>1.7</td>
<td>1.6</td>
</tr>
<tr>
<td>No previous use indicated</td>
<td>6.9</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\) AEDs classified as barbiturate, benzodiazepine, carbamazepine, hydantoin, valproate, or other.
VGB Reduces Seizure Frequency (Protocol-specified Primary Endpoint)
Study 025 (N = 174)

Median reduction from baseline in seizure frequency per 28 days

Baseline median

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline Median</th>
<th>Median Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>9.0</td>
<td>0.2</td>
</tr>
<tr>
<td>VGB 1 g/day</td>
<td>8.5</td>
<td>0.8</td>
</tr>
<tr>
<td>VGB 3 g/day</td>
<td>8.5</td>
<td>4.8</td>
</tr>
<tr>
<td>VGB 6 g/day</td>
<td>8.5</td>
<td>4.0</td>
</tr>
</tbody>
</table>

*p values vs placebo.

- Placebo vs VGB 1 g/day: *p = 0.1648*
- VGB 1 g/day vs VGB 3 g/day: *p = 0.0001*
- VGB 3 g/day vs VGB 6 g/day: *p = 0.0002*
VGB Reduces Seizure Frequency (Protocol-specified Primary Endpoint)
Study 024 (N = 182)

Baseline median

<table>
<thead>
<tr>
<th>Placebo</th>
<th>VGB 3 g/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.0</td>
<td>8.3</td>
</tr>
</tbody>
</table>

Median reduction from baseline in seizure frequency per 28 days

- Placebo: 1.5
- VGB 3 g/day: 2.8

$p = 0.0143$
VGB Can Produce Seizure Freedom
Study 025

Seizure freedom, percentage of patients

VGB Can Produce Seizure Freedom
Study 025

VGB 1 g/day: 2.2%
VGB 3 g/day: 12.2%
VGB 6 g/day: 11.6%

Placebo: 0%

*p values vs placebo.
VGB Efficacy Onset
Pooled Studies 025 and 024

- Placebo (n = 135)
- VGB 1 g/d (n = 45)
- VGB 3 g/d (n = 133)
- VGB 6 g/d (n = 43)

Proportion with 50% reduction from baseline in seizure rate

Weeks from baseline

0 2 4 6 8 10 12 14 16 18 20
### Multiple Studies Confirm VGB Efficacy

**Cochrane Meta-analysis**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Vigabatrin, n/N</th>
<th>Placebo, n/N</th>
<th>Weighted risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beran 1996</td>
<td>34/97</td>
<td>16/97</td>
<td></td>
</tr>
<tr>
<td>Bruni 2000</td>
<td>28/58</td>
<td>14/53</td>
<td></td>
</tr>
<tr>
<td><strong>Dean 1999/Dodrill 1995</strong></td>
<td>55/129</td>
<td>3/45</td>
<td></td>
</tr>
<tr>
<td><strong>French 1996/Dodrill 1993</strong></td>
<td>40/92</td>
<td>17/90</td>
<td></td>
</tr>
<tr>
<td>Gram 1985</td>
<td>8/21</td>
<td>2/21</td>
<td></td>
</tr>
<tr>
<td>Grunewald 1994</td>
<td>10/22</td>
<td>4/23</td>
<td></td>
</tr>
<tr>
<td>Loiseau 1986</td>
<td>9/19</td>
<td>1/19</td>
<td></td>
</tr>
<tr>
<td>McKee 1993</td>
<td>15/24</td>
<td>9/24</td>
<td></td>
</tr>
<tr>
<td>Rimmer 1984</td>
<td>14/24</td>
<td>1/24</td>
<td></td>
</tr>
<tr>
<td>Tartara 1986</td>
<td>9/20</td>
<td>0/21</td>
<td></td>
</tr>
<tr>
<td>Tassinari 1987</td>
<td>10/30</td>
<td>4/30</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>536</td>
<td>446</td>
<td>2.58 (1.87, 3.57)</td>
</tr>
</tbody>
</table>

Overview

- Clinical pharmacology
- Clinical development program
  - Efficacy in refractory complex partial seizures (CPS)
  - Safety
Adverse Events in ≥5% of VGB-Treated Patients and More Frequently Than Placebo
Studies 025 and 024

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Patients, n (%)</th>
<th>VGB n = 222</th>
<th>Placebo n = 135</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td></td>
<td>60 (27.03)</td>
<td>22 (16.30)</td>
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<tr>
<td>Somnolence</td>
<td></td>
<td>49 (22.07)</td>
<td>18 (13.33)</td>
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<tr>
<td>Dizziness</td>
<td></td>
<td>47 (21.17)</td>
<td>23 (17.04)</td>
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<tr>
<td>Nystagmus</td>
<td></td>
<td>34 (15.32)</td>
<td>12 (8.89)</td>
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<tr>
<td>Tremor</td>
<td></td>
<td>31 (13.96)</td>
<td>11 (8.15)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td></td>
<td>29 (13.06)</td>
<td>14 (10.37)</td>
</tr>
<tr>
<td>Vision blurred</td>
<td></td>
<td>25 (11.26)</td>
<td>7 (5.19)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td>23 (10.36)</td>
<td>10 (7.41)</td>
</tr>
<tr>
<td>Irritability</td>
<td></td>
<td>23 (10.36)</td>
<td>10 (7.41)</td>
</tr>
<tr>
<td>Memory impairment</td>
<td></td>
<td>21 (9.46)</td>
<td>4 (2.96)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td></td>
<td>21 (9.46)</td>
<td>7 (5.19)</td>
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<tr>
<td>Coordination abnormal</td>
<td></td>
<td>19 (8.56)</td>
<td>3 (2.22)</td>
</tr>
<tr>
<td>Diplopia</td>
<td></td>
<td>19 (8.56)</td>
<td>4 (2.96)</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td>19 (8.56)</td>
<td>11 (8.15)</td>
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<tr>
<td>Pharyngolaryngeal pain</td>
<td></td>
<td>19 (8.56)</td>
<td>7 (5.19)</td>
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<tr>
<td>Arthralgia</td>
<td></td>
<td>18 (8.11)</td>
<td>4 (2.96)</td>
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<tr>
<td>Weight increased</td>
<td></td>
<td>17 (7.66)</td>
<td>4 (2.96)</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td>16 (7.21)</td>
<td>8 (5.93)</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td>15 (6.76)</td>
<td>4 (2.96)</td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td></td>
<td>15 (6.76)</td>
<td>4 (2.96)</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td></td>
<td>15 (6.76)</td>
<td>9 (6.67)</td>
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<tr>
<td>Constipation</td>
<td></td>
<td>14 (6.31)</td>
<td>4 (2.96)</td>
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<tr>
<td>Back pain</td>
<td></td>
<td>13 (5.86)</td>
<td>3 (2.22)</td>
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<tr>
<td>Confusional state</td>
<td></td>
<td>13 (5.86)</td>
<td>1 (0.74)</td>
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<tr>
<td>General symptom</td>
<td></td>
<td>13 (5.86)</td>
<td>4 (2.96)</td>
</tr>
<tr>
<td>Asthenia</td>
<td></td>
<td>12 (5.41)</td>
<td>2 (1.48)</td>
</tr>
<tr>
<td>Disturbance in attention</td>
<td></td>
<td>12 (5.41)</td>
<td>1 (0.74)</td>
</tr>
</tbody>
</table>
## Serious Adverse Events Occurring More Frequently in VGB-Treated Patients

Studies 025 and 024

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Patients, n (%)</th>
<th></th>
<th></th>
<th>Patients, n (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VGB n = 222</td>
<td>Placebo n = 135</td>
<td></td>
<td>VGB n = 222</td>
<td>Placebo n = 135</td>
<td></td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>16 (7.21)</td>
<td>2 (1.48)</td>
<td></td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Status epilepticus</td>
<td>4 (1.80)</td>
<td>0</td>
<td></td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Convulsion</td>
<td>3 (1.35)</td>
<td>1 (0.74)</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3 (1.35)</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (0.45)</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Feeling drunk</td>
<td>1 (0.45)</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1 (0.45)</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Urosepsis</td>
<td>1 (0.45)</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Drug toxicity</td>
<td>1 (0.45)</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td>1 (0.45)</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Grand mal convulsion</td>
<td>1 (0.45)</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Simple partial seizures</td>
<td>1 (0.45)</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Abnormal behavior</td>
<td>1 (0.45)</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Completed suicide</td>
<td>1 (0.45)</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Confusional state</td>
<td>1 (0.45)</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>1 (0.45)</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Mood disorder due to a general medical condition</td>
<td>1 (0.45)</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Personality disorder</td>
<td>1 (0.45)</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Psychotic disorder due to a general medical condition</td>
<td>1 (0.45)</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>1 (0.45)</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 (0.45)</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
Overview

- Clinical pharmacology
- Clinical development program
  - Efficacy in refractory complex partial seizures (CPS)
  - Safety
MRI Assessment Overview

- 1983: Preclinical intramyelanic edema (IME)
  - Noted in rodents and dogs
- Late 1990s: Human concerns considered addressed
  - Prior sponsor review of MRIs
    - CPS: 7 trials in adults; 5 trials in pediatrics
    - No evidence of VGB-attributable MRI abnormalities
- 2006: Pearl - High T2 MRI signal abnormality reported in 3 patients with infantile spasms
2007: Ovation Repeat Review of MRIs

MRI Repeat review process

- Hard-copy MRIs for > 600 adult and pediatric patients
  - 2192 MRIs in database
  - 2024 MRIs were determinate
- Independent neuroradiologists
  - Masked double review with adjudication
# Results of CPS MRI Repeat Review—Consistent With Epilepsy Population

<table>
<thead>
<tr>
<th>MRI findings</th>
<th>VGB exposed</th>
<th>VGB naive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence (%)</td>
<td>14.2</td>
<td>13.1</td>
</tr>
<tr>
<td>95% CI</td>
<td>(11.5, 17.3)</td>
<td>(8.7, 18.7)</td>
</tr>
<tr>
<td>Incidence (%)</td>
<td>10.8</td>
<td>8.0</td>
</tr>
<tr>
<td>95% CI</td>
<td>(8.1, 13.9)</td>
<td>(4.2, 13.6)</td>
</tr>
</tbody>
</table>

Prevalence = Occurrence of ≥ 1 pre-specified MRI signal abnormality seen in a treatment period for T2, FLAIR, and/or diffusion-weighted imaging (DWI), irrespective of whether a baseline MRI was available.

Incidence = Occurrence of ≥ 1 pre-specified MRI signal abnormality on T2, FLAIR, and/or DWI among subjects with a determinate MRI at baseline which was free of pre-specified abnormalities.

Conclusion— VGB Does Not Cause MRI Abnormalities in Patients Treated for CPS

- No significant difference in prevalence or incidence of prespecified MRI abnormalities between VGB-exposed and VGB-naive
- Anatomic distribution of MRI abnormalities
  - Predominantly hemispheric white matter
  - Does not resemble pattern in IS patients or IME in animals
  - Consistent with literature reports of findings in epilepsy populations
Vigabatrin Efficacy and Safety Summary

- Unique MOA
- Effective with rapid onset
  - Decreases seizure frequency
  - Complete seizure freedom (7% - 12%)
  - Onset within 4 - 6 weeks
- Generally well tolerated
  - Common AEs (fatigue, dizziness, somnolence) similar to other AEDs
- MRI
  - No evidence of MRI abnormality or IME in refractory CPS patients
Sabril® (vigabatrin) Tablets for Refractory Complex Partial Seizures
Peripheral Visual Field Defect (pVFD) Assessment and Monitoring

Robert C. Sergott, MD
Director of Neuro-Ophthalmology
Professor of Ophthalmology and Neurology
Wills Eye Institute, Thomas Jefferson University
Vigabatrin pVFD

- Vigabatrin may produce a pVFD in some patients
- Detection and monitoring of pVFD requires regular assessments of visual function
- Will be able to detect peripheral defects comparable to glaucoma
  - Without loss of central vision
  - Tailor evaluation to patients’ cognitive function and cooperation
    - Confrontation, static, and kinetic perimetry
    - Electroretinogram (ERG)
    - Optical coherence tomography (OCT)
The Normal Extent of Visual Field

What we see when we hold our central vision steady on an object

Largest dimension (isopter) of visual field extends 90 degrees temporally and 60 degrees nasally superiorly and inferiorly
Classifications of pVFD

- **Mild** – not clinically significant (120° - 160°)
- **Moderate** – not clinically significant; can reliably detect change at the moderate level (60° - 120°)
- **Severe** – clinically significant (< 60°)

Constriction – concentric decrease in extent of field
## Current Practice of Ophthalmology Can Detect a Moderate pVFD (Glaucoma & VGB)

<table>
<thead>
<tr>
<th>Methodology</th>
<th>Age appropriateness&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confrontation visual field testing</td>
<td>All ages</td>
<td>Examiner interaction with patient; especially useful in young children and patients unable to perform formal perimetry</td>
</tr>
<tr>
<td>Kinetic target perimetry (Goldmann and automated)</td>
<td>≥ 9 yr</td>
<td>Suitable for patients who have shorter attention or poor visual acuity, but who can still cooperate and maintain fixation. <em>Tests both central and peripheral field</em></td>
</tr>
<tr>
<td>Static target Threshold perimetry</td>
<td>≥ 9 yr</td>
<td>Accurate, but threshold may vary in affected locations and requires good attention</td>
</tr>
<tr>
<td>Electroretinogram (ERG) light-evoked potential</td>
<td>All ages</td>
<td>Fall-back option for a patient that cannot perform perimetry; usually requires sedation in children. Limited availability</td>
</tr>
</tbody>
</table>

<sup>a</sup> Cognitive age.
Reliability of Perimetry Testing in Epilepsy Patients Compared to Glaucoma Patients

- Approximately 20% of epilepsy patients are unable to perform standard visual fields, according to Harding et al (2000)a

- Joint study from Detroit and Toronto demonstrated that only 25% - 34% of patients with glaucoma are unable to perform standard visual fieldsb

- Therefore, unreliable visual field testing in a small segment of patients is not a new or insurmountable problem for ophthalmologists

---

Electroretinogram Use for Infants and Adults Treated With Vigabatrin

- During ERG test, cells of retina (rods and cones) release tiny amounts of electricity in response to flashes of light.
- If we know exactly how much light enters the eye and how much electricity comes out, we can determine how rods and cones are working.
- To pick up electricity from retina, pupils are dilated, eyes dark-adapted, and a special contact lens is placed on surface of the eye.
ERG as a Complementary Study for Possible Visual Field Constriction

- b-wave amplitude appears to correlate with peripheral field constriction
- Review of the literature discloses occasional discrepancies between visual field testing and ERG
- Discrepancies likely due to unreliable visual field testing

Spectral Domain Optical Coherence Tomography

Use OCT to monitor retinal nerve fiber layer and macular thickness with vigabatrin use
# Activities Retained After Onset of pVFD

<table>
<thead>
<tr>
<th>Retained binocular field</th>
<th>Binocular Activities of daily living</th>
<th>Driving</th>
<th>Walking safely</th>
<th>Reading, watching TV, recognizing people</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild</strong> (120° - 160°)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Moderate</strong> (60° - 120°)</td>
<td>✓</td>
<td>+/-</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Severe</strong> (&lt; 60°)</td>
<td>✓</td>
<td>-</td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

- ✓ = Activities retained
- +/- = May or may not be affected

Develop adaptive strategies such as scanning

Ovation 2008 neuroophthalmologist panel.
# Summary of Testing Reliability for VGB-Induced pVFD

<table>
<thead>
<tr>
<th>pVFD severity</th>
<th>Confrontation</th>
<th>Kinetic perimetry</th>
<th>Automated kinetic perimetry</th>
<th>Static perimetry</th>
<th>ERG</th>
<th>OCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (120° - 160°)</td>
<td>−</td>
<td>+/−</td>
<td>+/−</td>
<td>+/−</td>
<td>+/−</td>
<td>+/−</td>
</tr>
<tr>
<td>Moderate (60° - 120°)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Severe (&lt; 60°)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

✓ = Reliable test  
+/− = May or may not be reliable

Ovation 2008 neuroophthalmologist panel.
Approved Medications With Potential Retinal/ Optic Nerve Toxicity—Acceptable Risk/Benefit Ratio

**Disruption of the retina and RPE**
- Phenothiazines
  - Thioridazine
  - Chlorpromazine
- Chloroquine derivatives
  - Chloroquine
  - Hydroxychloroquine
- Quinine sulfate
- Clofazimine
- Deferoxamine/Desferrioxamine

**Vascular occlusion**
- Quinine sulfate
- Ergot alkaloids
- Oral contraceptives

**Cystoid macular edema or retinal edema/folds**
- Nicotinic acid
- Corticosteroids – central serous retinopathy
- Oral contraceptives

**Crystalline retinopathy**
- Methoxyflurane
- Tamoxifen
- Canthaxanthine
- Nitrofurantoin
- Talc

**Miscellaneous**
- Chemotherapeutic agents
- Amiodarone
- Rifabutin
- Ethambutol, rifampin, methotrexate
- Anti-TNF agents for RA

Adapted from American Academy of Ophthalmology (AAO) Focal Point Update Series.
Visual Acuity and Vigabatrin

- One study has been cited by the Agency that reports mild visual acuity changes with VGB

- Several issues make this finding difficult to interpret
  - Visual acuity was not reported to be done with standardized luminance
  - No refractions were performed as is required for standardized clinical trials. A pinhole test is not a reliable substitute for an expert refraction.
  - “Several older” patients were reported to have mild cataracts
  - No central scotomas (central visual deficits) were detected with visual field testing

- 12/32 had visual acuity ranging from 20/25 to 20/60, a level of vision that will permit those patients to read normal size type, recognize faces, and drive in many states

- 20/32 had visual acuity of 20/20 or better

---

Summary

- We understand that some patients treated with VGB will develop pVFD
- Currently available ophthalmologic testing methods can reliably detect moderate pVFD
- Periodic ophthalmologic examinations should be required in VGB treated patients to prevent clinically meaningful pVFD and to assess the benefit/risk ratio of this medication
Sabril® (vigabatrin) Tablets for Refractory Complex Partial Seizures Peripheral Visual Field Defect (pVFD) Characterization

Stephen M. Sagar, MD
Medical Director
Ovation Pharmaceuticals, Inc.
VGB-Induced pVFD

- Clinical features
- Study 4020 design and limitations
- Frequency of pVFD
- Severity and impact on the patient
- Risk factors
- Time course
- Visual acuity
- Conclusions and recommendations
VGB-Induced pVFD

- VGB can cause bilateral, concentric peripheral constriction of the visual fields, often more marked in the nasal than the temporal visual field
- Preponderance of the evidence supports no effect on visual acuity
  - Rare reports with confounding factors and minimal effect
- The retina is the site of injury
Children: 8 - 12 years old (n = 126)
Adults: > 12 years old (n = 398)

Group 1
ON VGB ≥ 6 months
Patients to continue or discontinue VGB
n = 187

Group 2
On VGB ≥ 6 mo | Off VGB
Patients could resume VGB
n = 199

Group 3
Never on VGB
Patients could initiate VGB therapy
n = 138

VF testing every 4 - 6 months

Time 0
Study Design
Study 4020

- Perimetryst, either static or kinetic or both, every 4 to 6 months for up to 3 years
- Primary outcome measure, BCPC, was based on central review of perimetryst by a single reader, Dr. John Wild, masked to treatment
- Ovation performed post-hoc, quantitative analysis based on 347/524 subjects who underwent Goldmann perimetry
Limitations
Study 4020

- BCPC determination based on overall clinical assessment of one reader
- Few Group III subjects began VGB on-study
- Few observations with short durations of drug exposure
- Specifications for perimetries relaxed during the study
- Subject selection and discontinuations may impact data interpretation
# Prevalence of BCPC

**Study 4020**

<table>
<thead>
<tr>
<th>Group</th>
<th>Prevalence, % (95% CI)</th>
<th>Median exposure, yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult First conclusive perimetry</td>
<td>27.8 (20.2, 29.0)</td>
<td>3.2</td>
</tr>
<tr>
<td>Adult Confirmed BCPC</td>
<td>24.6 (19.8, 29.9)</td>
<td>4.7</td>
</tr>
<tr>
<td>Children Confirmed BCPC</td>
<td>15.3 (5.6, 19.9)</td>
<td>4.3</td>
</tr>
<tr>
<td><strong>Highest prevalence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult Group I ≥ 1 BCPC</td>
<td>45.6 (37.5, 54.0)</td>
<td>5.2</td>
</tr>
<tr>
<td>Adult Group I Confirmed BCPC</td>
<td>32.9 (25.4, 41.0)</td>
<td>5.4</td>
</tr>
</tbody>
</table>
Incidence of BCPC
Study 4020—Initially BCPC-free Cohort

The risk of developing a new pVFD while taking VGB is ~ 8% per year for adults during treatment with VGB for CPS

Includes all evaluable patients exposed to VGB on or before their final perimetry.
Visual Field Impairment
Study 4020 (N = 347)

- **Unimpaired**: > 160° binocular visual field, > 80° monocular temporal field retained
- **Mild**: 120 - 160° binocular visual field, 60 - 80° monocular temporal field retained
- **Moderate**: 60 - 120° binocular visual field, 30 - 60° monocular temporal field retained
- **Severe**: < 60° binocular visual field, < 30° monocular temporal field retained
Severity of pVFD—Retained Visual Field Study 4020—Goldmann Perimetry

- Duration of VGB exposure, years
- Patients, %
  - > 160 unimpaired
  - 120 - 160 mild
  - 60 - 120 moderate
  - < 60 severe

- Duration of VGB exposure, years
  - n = 84
  - > 0 - 1
  - n = 57
  - > 1 - 2
  - n = 43
  - > 2 - 3
  - n = 33
  - > 3 - 4
  - n = 35
  - > 4 - 6
  - n = 46
  - > 6 - 8
  - n = 32
  - > 8
  - n = 29
### Impact on the Patient

**Study 4020—Patients With Goldmann Perimetry**

<table>
<thead>
<tr>
<th>Population</th>
<th>Unimpaired (&gt; 160), %</th>
<th>Mild (120 to 160), %</th>
<th>Moderate (60 to &lt; 120), %</th>
<th>Severe (&lt; 60), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>34.3</td>
<td>36.8</td>
<td>54.2</td>
<td>66.7</td>
</tr>
<tr>
<td></td>
<td>n = 99</td>
<td>n = 171</td>
<td>n = 48</td>
<td>n = 6</td>
</tr>
<tr>
<td>Children</td>
<td>12.5</td>
<td>23.1</td>
<td>47.1</td>
<td>66.7</td>
</tr>
<tr>
<td></td>
<td>n = 24</td>
<td>n = 52</td>
<td>n = 17</td>
<td>n = 3</td>
</tr>
</tbody>
</table>

Unless the pVFD becomes severe, it is generally asymptomatic and has minimal impact on quality of life.
VGB-Induced pVFD—Risk Factors

- Risk of pVFD increases with
  - Duration of exposure
  - Cumulative dose
  - Daily dose
In the majority of cases, VGB-induced pVFD is a slow process, generally becoming detectable by perimetry only after several years of exposure in adults.

Progression to a severe deficit (loss of < 60 degrees of temporal visual field) generally requires ≥ 3 years of exposure.
All Patients With Goldmann Perimetry Study 4020

Degrees in binocular field

VGB exposure, years

- 0
- > 0 - 1
- > 1 - 2
- > 2 - 3
- > 3 - 4
- > 4 - 6
- > 6 - 8
- > 8

n = 84 n = 57 n = 43 n = 33 n = 35 n = 46 n = 32 n = 29
## Change of Temporal Field On VGB
### Study 4020—Patients With Goldmann Perimetry

<table>
<thead>
<tr>
<th>Cohort</th>
<th>VGB status</th>
<th>Subjects</th>
<th>Change, degrees/year of exposure</th>
<th>Standard error</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult I and III</td>
<td>On</td>
<td>91</td>
<td>-1.61</td>
<td>0.42</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Adult I and II</td>
<td>Off</td>
<td>138</td>
<td>-1.65</td>
<td>0.45</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Adult III</td>
<td>Off</td>
<td>66</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Child I and III</td>
<td>On</td>
<td>33</td>
<td>-0.94</td>
<td>0.95</td>
<td>0.330</td>
</tr>
<tr>
<td>– Child I and III On</td>
<td>On &lt; 7.5 years</td>
<td>29</td>
<td>-0.04</td>
<td>0.73</td>
<td>0.961</td>
</tr>
<tr>
<td>– Child I and III On</td>
<td>On ≥ 7.5 years</td>
<td>4</td>
<td>-11.70</td>
<td>3.25</td>
<td>0.035</td>
</tr>
<tr>
<td>Child I and II</td>
<td>Off</td>
<td>43</td>
<td>-1.66</td>
<td>0.63</td>
<td>0.012</td>
</tr>
<tr>
<td>Child III</td>
<td>Off</td>
<td>17</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
VGB-Induced pVFD—Time Course

- Onset of pVFD detectable by perimetry is, with uncommon exceptions, after > 1 year of exposure
# VGB-Induced pVFD Onset < 1 Year—Clinical Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Earliest onset</th>
<th>n/N</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 4020</td>
<td>9 mo</td>
<td>5/58</td>
<td>Confirmed BCPC</td>
</tr>
<tr>
<td>R003</td>
<td>2 mo</td>
<td>1/25</td>
<td>Abnormal baseline exam</td>
</tr>
<tr>
<td>Pooled cohort analysis</td>
<td>&lt; 1 yr</td>
<td>2/104</td>
<td></td>
</tr>
</tbody>
</table>
Pooled Cohort Analysis

- Cross-sectional study
- Perimetry method and grading system not described
- Incidence analyses invalid
  - Wrong denominators used for subjects exposed
  - Only 2/104 subjects with VFD after ≤ 1 year VGB exposure
VGB-Induced pVFD Onset < 1 Year—Literature

<table>
<thead>
<tr>
<th>Source</th>
<th>Earliest onset</th>
<th>n/N</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kiratli &amp; Turkcuoglu (2001)</td>
<td>6 mo</td>
<td>1/1</td>
<td>No baseline, ERG normal</td>
</tr>
<tr>
<td>Malmgren et al. (2001)</td>
<td>4 mo</td>
<td>1/99</td>
<td>Abnl = &lt; 80 deg temp, &lt; 40 deg nasal</td>
</tr>
<tr>
<td>Riise et al. (2003)</td>
<td>1 yr</td>
<td>1/31</td>
<td></td>
</tr>
<tr>
<td>Schmitz et al. (2002)</td>
<td>9 mo</td>
<td>1/29</td>
<td>Prospective study</td>
</tr>
<tr>
<td>Wild et al. (1999)</td>
<td>1 yr</td>
<td>1/42</td>
<td></td>
</tr>
<tr>
<td>Fechtner et al. (2008)</td>
<td>NA</td>
<td>0/18</td>
<td>Prospective study, 8 week exposure</td>
</tr>
</tbody>
</table>

VGB-Induced pVFD
Onset < 1 Year—Postmarketing

- Database reviewed through 15 May 2008
- ‘VFD’ reported: 980 cases, 29 cases (6.4%) within 1 yr of VGB start
  - 23 had no documentation of a pVFD
  - 6 possible cases
    - 5 had inadequate documentation of the pVFD
    - 1 documented case: 19 yo female, normal baseline perimetry, pVFD at 5 weeks of VGB, resolved at 2 months after stopping VGB
VGB-Induced pVFD Time Course

- With some possible exceptions, VGB-induced pVFD neither reverses nor progresses after drug is discontinued
## Change in Temporal Field Off VGB

Study 4020—Patients With Goldmann Perimetry

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Patients</th>
<th>Change, degrees/year of exposure</th>
<th>Standard error</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult I and II</td>
<td>138</td>
<td>-0.15</td>
<td>0.50</td>
<td>0.7773</td>
</tr>
<tr>
<td>Adult III</td>
<td>66</td>
<td>-1.32</td>
<td>0.65</td>
<td>0.050</td>
</tr>
<tr>
<td>Child I and II</td>
<td>43</td>
<td>2.05</td>
<td>1.24</td>
<td>0.108</td>
</tr>
<tr>
<td>Child III</td>
<td>17</td>
<td>1.44</td>
<td>1.36</td>
<td>0.317</td>
</tr>
</tbody>
</table>
Does VGB Affect Visual Acuity?

- The vast preponderance of the evidence indicates that VGB has no detectable long-term effects on visual acuity.
- Few reports:
  - Degree of impact minor
  - Confounded by other factors
  - Some fail to distinguish reversible pharmacologic effects while taking drug from permanent effects.
### Visual Acuity—Glasgow Data

<table>
<thead>
<tr>
<th>Right eye</th>
<th>On VGB</th>
<th>Prior VGB</th>
<th>GABA AED</th>
<th>Non GABA AED</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>56</td>
<td>49</td>
<td>46</td>
<td>53</td>
</tr>
<tr>
<td>Median</td>
<td>0.00</td>
<td>0.05</td>
<td>0.08</td>
<td>0.00</td>
</tr>
<tr>
<td>Mean</td>
<td>0.07</td>
<td>0.08</td>
<td>0.04</td>
<td>0.10</td>
</tr>
<tr>
<td>Std Dev</td>
<td>0.15</td>
<td>0.14</td>
<td>0.35</td>
<td>0.42</td>
</tr>
<tr>
<td>Range</td>
<td>$-0.1 - 0.8$</td>
<td>$-0.1 - 0.6$</td>
<td>$-2.0 - 0.7$</td>
<td>$-0.2 - 3.0$</td>
</tr>
</tbody>
</table>

No differences between VGB and non-VGB treatment groups
## Visual Acuity and Color Vision

### Literature Reports

<table>
<thead>
<tr>
<th>Author</th>
<th>Patient population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malmgren et al (2001)</td>
<td>99 VGB</td>
<td>19 w/VFD, VA WNL in all</td>
</tr>
<tr>
<td>Krauss et al (2003)</td>
<td>32 VGB, 12 TGB, 14 control</td>
<td>No difference between groups in VA</td>
</tr>
<tr>
<td>McDonagh et al (2003)</td>
<td>32 VGB (&gt; 3 yr)</td>
<td>No difference in VA, color vision</td>
</tr>
<tr>
<td></td>
<td>30 matched controls</td>
<td></td>
</tr>
<tr>
<td>Kalviainen et al (1999)</td>
<td>32 VGB (mean 69 mos)</td>
<td>40% VFD in VGB, 0 in CBZ (Goldmann), VA normal</td>
</tr>
<tr>
<td></td>
<td>18 CBZ</td>
<td></td>
</tr>
<tr>
<td>Lawden et al (1999)</td>
<td>31 VGB</td>
<td>12 w/VFD (Humphries), VA and color WNL in 11</td>
</tr>
<tr>
<td>Wild et al (1999)</td>
<td>42 VGB</td>
<td>39 w/BCPC (Goldmann), VA, color vision unaffected</td>
</tr>
<tr>
<td>Miller et al (1999)</td>
<td>39 VGB</td>
<td>20 VGB w/ VA 20/20 or better; 12 VGB w/ VA 20/25 to 20/60, controls w/ NL VA, 19 VGB w/ color vision 3.5 to 8.5 (of 10)</td>
</tr>
<tr>
<td></td>
<td>11 control</td>
<td></td>
</tr>
</tbody>
</table>

Implications for Monitoring Vision

- Because the retinal effects may be asymptomatic, ongoing benefit/risk assessments for patients taking VGB require periodic ophthalmologic examinations.
Visual Function Monitoring
Mandatory Visual Testing

- Ophthalmological testing at baseline and then every 6 months while taking drug
- Increase in frequency to every 3 months if pVFD detected
- Use methods appropriate for cognitive ability
  - Confrontation
  - Kinetic and/or static perimetry
  - ERG
  - OCT
VGB-Induced pVFD Summary

- No effect on visual acuity
- VGB is associated with a distinctive bilateral constriction of the visual field (pVFD)
- Based on Study 4020, fewer than 3% will develop a severe restriction of peripheral vision over the first 4 - 5 years of exposure
- Generally progresses slowly, allowing effective monitoring of visual function
- Cognition and age-appropriate methods exist to monitor visual function
Sabril® (vigabatrin) Tablets and Powder for Oral Solution
Risk Evaluation and Mitigation Strategy (REMS)

Tim Cunniff, PharmD
Vice President, Global Regulatory Affairs, Pharmacovigilance & Clinical Quality Assurance
Ovation Pharmaceuticals, Inc.
Sabril REMS Goals

- To minimize the risk of Sabril-induced peripheral visual field defect (pVFD)
- To detect Sabril-induced pVFD before it results in a clinically meaningful restriction of the patient’s peripheral vision
- To ensure regular ophthalmologic monitoring to facilitate ongoing benefit-risk assessments
Sabril REMS Elements

**Medication Guide**
- Risks explained in patient-friendly language via Medication Guide
  - pVFD
  - MRI
  - Suicidality
- Dispensed with every Rx

**Communication Plan**
- Dear Healthcare Provider Letter
  - pVFD
  - MRI
- Physician education
  - pVFD
  - MRI
- Patient/Caregiver education
  - pVFD
  - MRI

**Elements to Assure Safe Use**
- Mandatory SHARE registration
- Restriction of initial Rx to neurologists
- Controlled drug distribution
- Enforced benefit/risk assessment after evaluation phase
- Visual testing reminder system
- Enforced ophthalmologic monitoring
- Sabril registry
Medication Guide

- To provide information to the patient/caregiver about the risks (ie, pVFD, MRI, and AED suicidality) associated with Sabril therapy
- Written in patient-friendly language
- Reviewed and discussed with the patient/caregiver multiple times during the prescribing and dispensing process
- Provided with each prescription fill

MEDICATION GUIDE
Sabril® (vigabatrin) Tablet for Complex Partial Seizures in Adults
(Pronounced as Say-bril)

To use Sabril appropriately you should:
- Be aware that Sabril may cause a serious vision problem in some people.
- Read this Medication Guide to understand the potential benefits and potential risks of Sabril therapy.
- Discuss and sign the Patient-Physician Agreement if you agree.
- Report any side effects of Sabril to your doctor immediately.
- Visit your doctor regularly to re-evaluate if the benefits of Sabril continue to outweigh any risks.

Read this Medication Guide carefully. Your doctor may require you to sign a Patient-Physician Agreement before you start taking Sabril. Read the Medication Guide you receive with each Sabril refill as it may contain new information. This Medication Guide does not take the place of talking with your doctor.

1. WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT Sabril?

About one-quarter of adults (about 1 out of 4) and 15% of children (about 1 out of 7) who take Sabril may lose some peripheral vision. Peripheral vision is what you use to see out of the corner of your eye and at the very top or bottom. Sabril does not change central vision, which is the vision you use to read or watch television. People who have a peripheral vision problem may not be able to see things by their nose or an object to the side without turning their head.

In adults who get this vision problem after taking Sabril, the earliest it happened in clinical studies was after taking Sabril for 12 months. The amount of vision loss is different in everyone, but usually, people who develop the problem may lose about one-fifth (1/5) of their side vision. The problem develops slowly over many weeks to months. If you get this vision problem, it does not go away. There is no way to treat this vision problem. If you stop taking Sabril, the chance of getting the vision problem goes away. You should tell your doctor immediately if you notice any changes to your vision.

Your doctor will recommend eye tests that should be done when you start taking Sabril and at certain times while you are still taking it.
WARNING: PERIPHERAL VISUAL FIELD DEFECT (VFD)

A peripheral Visual Field Defect (VFD) may occur in some patients taking Sabril. This peripheral VFD is characterized as a bilateral concentric peripheral constriction, usually in an arcuate or paracentral configuration. Central vision, including color vision and visual acuity, are not affected. The risk for developing peripheral VFD increases with total dose and duration of use. The peripheral VFD does not appear to reverse after discontinuation of Sabril. In rare cases, a peripheral VFD may develop after discontinuation. The majority of patients with the peripheral VFD are asymptomatic; therefore, appropriate visual testing is needed for detection. It is recommended that ophthalmologic testing be performed in adults receiving Sabril at baseline and at 6 month intervals [see WARNINGS AND PRECAUTIONS, Peripheral Visual Field Defect (5.1)].

Sabril should only be used when the potential benefits outweigh the potential risk for developing the peripheral VFD. If meaningful seizure improvement is observed, the benefits and risk should be periodically assessed for the duration of therapy.
Elements to Assure Safe Use

Prescribing → Dispensing → Treatment

- Mandatory neurologist (initial Rx) & physician registration with attestation
  - Mandatory patient registration
  - Mandatory benefit/risk assessment before maintenance phase treatment

- Controlled Drug Distribution System (SHARE)
  - Central call center with network of select specialty pharmacies

- Reminder system for visual testing
  - Enforced ophthalmologic monitoring for CPS patients

Sabril Registry
Enforced Benefit/Risk Assessment and Enforced Ophthalmologic Monitoring for Patients With CPS

**Evaluation phase**
- Assessment for improvement in CPS seizure control
- Initiate therapy and baseline pVFD test
- Taper off VGB if no clinical improvement

**Maintenance phase**
- Visual test reminders
- 6-month pVFD test
- Taper off VGB if ophthalmologic testing not done
- 12-month pVFD test

**Months**
1 2 3 4 5 6 7 8 9 10 11 12

**Increasing cumulative risk for pVFD**

pVFD = Peripheral visual field defect; CPS = Complex partial seizures.
Sabril Registry

- Data collection
  - Physician Attestation Form
  - Treatment Initiation Form
  - Treatment Maintenance Form
  - Ophthalmologic Assessment Form

- Annual reporting
  - Prescriber
    - Specialty, practice setting
  - Patient
    - Demographics, diagnosis, prior and current AEDs, dosing information, effectiveness (progression to treatment maintenance phase)
    - Ophthalmologic testing data (pVFD frequency, onset, severity, progression)
Assessment of Sabril REMS Effectiveness

- Data from Sabril Registry
- Physician and Patient/Caregiver Knowledge, Attitude and Behavior Surveys
  - 1 yr, 2 yr, 3 yr, 7 yr
- Pharmacovigilance Information
  - Periodic Adverse Event Reports: Quarterly \( \times 3 \) years then annually
  - Expedited reporting of serious liver injury cases
- Assessment results will be discussed with FDA and REMS modifications implemented as appropriate
Sabril® (vigabatrin) Tablets for Refractory Complex Partial Partial Seizures

Benefit/Risk Assessment

Roger J. Porter, MD
Adjunct Professor of Neurology
University of Pennsylvania, Philadelphia, PA
Adjunct Professor of Pharmacology
Uniformed Services University of the Health Sciences
Bethesda, MD
Sabril (vigabatrin) Tablets
CPS Benefit/Risk Assessment

I. Patients with refractory complex partial seizures (CPS) have a devastating disorder

II. VGB has important benefits

III. VGB has some risks; these risks are manageable
Complex Partial Seizures Are the Most Common Type of Seizure

- CPS 36%
- Refractory CPS
- Simple partial 14%
- Other Generalized 8%
- Other 3%
- Myoclonic 3%
- Absence 6%
- Generalized tonic-clonic 23%
- Partial unknown 7%
- Unclassified 3%

Morbidity/Mortality of Refractory CPS

- **Mortality rate** (in refractory seizures):
  - 4 - 7 times higher than general population

- **Injury rates**:
  - From 1 per 20 person-yr to 1 per 3 person-yr

Morbidity/Mortality of Refractory CPS

- Exacerbated by poor seizure control\(^a\)
  - Frequent seizures = decreased quality of life\(^a\)
  - Refractory CPS = increased risk of accidents and injuries vs general population\(^b\)
  - Refractory epilepsy associated with SUDEP and suicide\(^b,c\)

SUDEP = Sudden unexpected death in epilepsy.
Treating Refractory Epilepsy Patients

- Some drugs work better in some patients
- Physicians cannot predict most effective drug for a specific patient
- Physicians use trial and error
  - Most drugs eventually attempted

Sabril (vigabatrin) Tablets

CPS Benefit/Risk Assessment

I. Patients with refractory complex partial seizures (CPS) have a devastating disorder

II. VGB has important benefits

III. VGB has some risks; these risks are manageable
Benefits of VGB as Add-on Therapy

- Substantial numbers of patients respond to VGB
- Demonstrated efficacy
  - Significant reduction in seizures
    - Clinical trial efficacy comparable to other AEDs
    - Freedom from seizures (7% - 12%)
    - Rapid onset of efficacy
- VGB generally well-tolerated
  - As with most other AEDs, the most common dose-related AEs are CNS-related

AED = Antiepileptic drug; AE = Adverse event; CNS = Central nervous system.
Sabril (vigabatrin) Tablets
CPS Benefit/Risk Assessment

I. Patients with refractory complex partial seizures (CPS) have a devastating disorder

II. VGB has important benefits

III. VGB has some risks; these risks are manageable
Peripheral visual field defect (pVFD)

- Well-characterized
- Can be effectively monitored
- Nonresponders can be discontinued early, thus limiting likelihood of exposure to risk
Enforced Benefit/Risk Assessment and Enforced Ophthalmologic Monitoring for Patients With CPS

Assessment for improvement in CPS seizure control

Evaluation phase

Initiate therapy and baseline pVFD test

Months

1 2 3 4 5 6 7 8 9 10 11 12

Taper off VGB if no clinical improvement

Taper off VGB if ophthalmologic testing not done

Maintenance phase

Visual test reminders

6-month pVFD test

Increasing cumulative risk for pVFD

Visual test reminders

12-month pVFD test

pVFD = Peripheral visual field defect; CPS = Complex partial seizures.
Benefit/Risk of VGB Therapy in Adult Patients With Refractory CPS

- Effective option for decreasing/eliminating refractory CPS
- Opportunity exists to evaluate efficacy early, thus limiting exposure to pVFD risk
- Benefit: Risk favors use of VGB as adjunctive therapy for adult patients with refractory CPS who have inadequately responded to alternative treatments and for whom the potential benefits outweigh the potential risk of developing pVFD
Vigabatrin and OCT

- Cross-sectional, prospective observational design – right eye used
  - Group I – 13 patients VGB and field loss
  - Group II – 8 patients VGB, normal fields
  - Group III – 14 patients carbamazepine monotherapy
  - Group IV – 20 normal individuals, no epilepsy
  - Group V – 7 patients valporate monotherapy

- Perimetry
  - 135 point full field screening followed by threshold 30-2 with and FASTPAC strategy

Figure 3. The average retinal nerve fiber layer thickness (in micrometers) for the complete 360° scan derived by OCT as a function of (top) duration of therapy (years) with vigabatrin and (bottom) cumulative dose of vigabatrin (kilograms) for the patients with vigabatrin-attributed visual field loss (Group I; diamonds) and for the patients exposed to vigabatrin but with normal fields (Group II; circles). Note that the cumulative dose could not be determined accurately in one patient in Group II, and the value has been omitted from Figure 3 (bottom).

Wild JM, et al. IOVS. 2006;47:917-924.
Retinal Nerve Fiber Layer Thickness Derived by OCT  
Wild JM, et al. (2006)

<table>
<thead>
<tr>
<th>Group</th>
<th>Proportion Male: Female</th>
<th>Age (SD) (y)</th>
<th>Duration of Epilepsy (SD) (ys)</th>
<th>Duration of Vigabatrin Therapy (SD) (kg)</th>
<th>Cumulative Dose of Vigabatrin (SD) (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>7:6</td>
<td>42.9 (8.9)</td>
<td>27.3 (10.8)</td>
<td>10.1 (1.9)</td>
<td>7.8 (2.7)</td>
</tr>
<tr>
<td>II</td>
<td>8:0</td>
<td>40.1 (10.8)</td>
<td>25.9 (16.8)</td>
<td>7.3 (1.2)</td>
<td>6.1 (1.5)</td>
</tr>
<tr>
<td>III</td>
<td>3:11</td>
<td>41.2 (8.8)</td>
<td>19.5 (15.3)</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>IV</td>
<td>5:15</td>
<td>39.7 (12.3)</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>V</td>
<td>4:3</td>
<td>35.9 (11.2)</td>
<td>21.3 (14.8)</td>
<td>Nil</td>
<td>Nil</td>
</tr>
</tbody>
</table>

Data are the group mean ± SD.

Wild JM, et al. IOVS. 2006;47:917-924.
Percent of Patients Achieving $\geq$ 50% Reduction in Seizures by Number of Failed AEDs at Baseline$^a$

Studies 024 and 025

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>3 g/day VGB</th>
<th>6 g/day VGB</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - 3 failed AEDs Study 024</td>
<td>10</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td>4 - 6 failed AEDs Study 024</td>
<td>10</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td>1 - 3 failed AEDs Study 025</td>
<td>20</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>4 - 6 failed AEDs Study 025</td>
<td>20</td>
<td>50</td>
<td>60</td>
</tr>
</tbody>
</table>

$^a$ Failed for any reason.