INTRODUCTION

Approximately three million Americans of all ages are affected with seizure disorders, and approximately 200,000 new cases of seizures and epilepsy are diagnosed each year. Indirect and direct costs are estimated at $15.5 billion annually.

Seizures are caused by abnormal electrical disturbances in the brain. There are several types of seizures. Two catastrophic forms of epilepsy include complex partial seizures, which occur in more than one-third of all cases, and infantile spasms, which usually strike infants in their first year of life. Partial (focal or localized) seizures affect a limited area of the brain and may be simple or complex. Although awareness and memory are not affected in simple partial seizures, complex partial seizures affect the patient’s awareness and memory of events before, during, and immediately after the seizure; they also affect the patient’s behavior.

Infantile spasms, a component of West syndrome, typically affect patients between four and eight months of age. There may be a sudden bending forward of the body, with stiffening of arms and legs. Some children arch their backs as they extend their arms and legs. Seizures may occur upon awakening or even after feeding, often in clusters of up to 100 spasms at a time; they usually stop by the time the child is five years of age but may progress to other seizure disorders.

CHEMISTRY AND PHARMACOLOGY

Vigabatrin (Sabril, Lundbeck, formerly Ovation) is commercially available in tablet form and as an oral solution. The tablets are indicated as an adjunctive therapy for adults with refractory complex partial seizures who have not responded adequately to several treatments. In August 2009, the oral solution was approved as the only medication in the U.S. for patients with infantile spasms.

Vigabatrin was first approved in Europe and Canada. Its chemical name is (±) 4-amino-5-hexenoic acid. The structural formula is \( 	ext{C}_6\text{H}_{11}\text{NO}_2 \), and the molecular weight is 129.16.

The drug’s mechanism of antiseizure effect is believed to result from its ability to inhibit gamma-aminobutyric acid transaminase (GABA-T), the enzyme responsible for the metabolism of the inhibitory neurotransmitter GABA. This step results in increased levels of GABA in the brain synapses. Seizures are thought to result from low levels of GABA in the central nervous system (CNS).

PHARMACOKINETICS AND PHARMACODYNAMICS

Vigabatrin is absorbed orally. Its bioavailability is 50% with the S-enantiomer and 65% with the R-enantiomer. It may be taken with or without food. Vigabatrin is not protein-bound, and it is distributed widely throughout the body with a mean steady-state volume of distribution (\( V_d \)) of 1.1 L/kg (coefficient of variance, 20%).

No significant hepatic metabolism occurs with vigabatrin, although it is considered to be an inducer of cytochrome P450 2C9. Vigabatrin is excreted extensively via the kidneys, with an elimination half-life of 7 to 7.5 hours in adults and 5.7 hours in infants. Hemodialysis can reduce the drug’s plasma concentration by approximately 40 to 60%.

CLINICAL TRIALS

Seizures in Adults

Two multicenter, double-blind, randomized, placebo-controlled, parallel-group clinical trials of 357 patients have shown the efficacy of vigabatrin as an adjunctive therapy in adults 18 to 60 years of age with complex partial seizures, with or without secondary generalization. To be enrolled, patients had to be following an adequate and stable anticonvulsant dose regimen and must have failed to respond to a regimen of phenytoin (Dilantin, Pfizer) or carbamazepine (e.g., Carbatrol, Shire; Tegretol, Novartis). At baseline, patients had a history of eight seizures per month for a median of approximately 20 years. The primary efficacy outcome was a reduction in the mean monthly frequency of complex partial seizures and partial seizures with secondary generalization, compared with the baseline value, at the study’s end.

Study 1. The first study, with a total of 174 patients, consisted of an eight-week baseline period, followed by an 18-week treatment period. During the treatment phase, patients received placebo or viga-
batrin 1 g/day (n = 45), 3 g/day (n = 41), or 6 g/day (n = 43), given in two divided doses. The dosage was titrated upward per protocol until the assigned dose was achieved. The median monthly frequency of seizures, from the baseline to the end of the study, was decreased from 9 to 8.8 events in the placebo group of patients, from 8.5 to 7.7 events in the group receiving 1 g/day, from 8.5 to 3.7 events in the group receiving 3 g/day, and from 8.5 to 4.5 events in the group receiving 6 g/day (P < 0.05 for the 3-g/day and 6-g/day groups, compared with placebo).

No statistically significant differences between the 6-g/day and 3-g/day doses were observed. A 50% or greater reduction in seizure frequency was achieved in approximately 51% of patients receiving vigabatrin 6 g/day and in 53% of patients receiving 3 g/day, compared with 9% of patients receiving placebo.

**Study 2.** In this trial, an eight-week baseline period was followed by a 16-week treatment period; 183 patients were randomly assigned, and 182 were assessed for the medication’s efficacy. Ninety patients received placebo, and 92 patients received vigabatrin, with the dose titrated to 3 g/day. The median monthly frequency of complex partial seizures, from baseline to the study’s end, was decreased from 9 to 7.5 seizures in those receiving placebo and from 8.3 to 5.5 seizures in patients receiving vigabatrin (P < 0.05). Approximately 39% of the vigabatrin patients and 21% of the placebo patients achieved a 50% or greater reduction in the frequency of seizures.7,8

**Seizures in Infants**

Two multicenter, randomized, controlled studies involving a total of 261 patients have shown efficacy for vigabatrin in managing infantile spasms.

**Study 1.** A low-dose/high-dose, parallel-group study enrolled 221 children younger than two years of age with new-onset infantile spasms. The caregivers were unaware of the dose a child was receiving. During a 14- to 21-day partially blind phase, patients received either low-dose vigabatrin (18–36 mg/kg per day) or high-dose vigabatrin (100–148 mg/kg per day). The dosage was titrated over a period of seven days, followed by a constant-dose phase for seven days.

If patients became free of spasms on or before day 14, they received an additional constant dose for seven days. The proportion of patients who became spasm-free for seven consecutive days within the first 14 days of vigabatrin therapy (the primary study outcome) was 15.9% (17 of 107 patients) in the high-dose group and 7% (8 of 114 patients) in the low-dose group (P = 0.0375).

**Study 2.** In a double-blind, placebo-controlled, parallel-group study of 40 patients, the pretreatment phase consisted of two to three days, followed by a five-day double-blind treatment phase. During this phase, patients received placebo or vigabatrin 50 mg/kg per day, with the dose titrated upward to 150 mg/kg per day.

The primary efficacy outcome was the average percentage of change in the frequency of daily spasms, evaluated during a predefined and consistent two-hour window. The investigators compared the baseline value with that of the last two days of the five-day treatment phase. No statistically significant differences were noted in the average frequency of spasms during the two-hour evaluation window; however, when a 24-hour evaluation window was used, the difference in the overall percentage of reductions in spasms was statistically significant (68.9% with vigabatrin, 17% with placebo; P = 0.03).

Fejerman et al. In a prospective study of infantile spasms in 116 patients with West syndrome, 29.3% of patients with the symptomatic form became seizure-free after treatment, whereas 61.8% of treated patients with the cryptogenic (idiopathic) form were seizure-free.12 Approximately 18% of the patients with symptomatic West syndrome and 12% of those with cryptogenic West syndrome did not respond to treatment. The mean effective dose was 150 mg/kg per day. Normalization of electroencephalogram findings was observed in 52.6% of the patients with the symptomatic type and in 100% of the patients with the cryptogenic type.12

**DRUG–DRUG INTERACTIONS**7,8

Total plasma levels of phenytoin may be decreased when vigabatrin is coadministered, probably a result of induction of CYP 2C enzymes. Dose adjustments of phenytoin may be considered, but they are not routinely recommended. Phenobarbital and valproate sodium (Abbott) plasma levels are also decreased with the coadministration of vigabatrin and do not appear to be clinically significant.

Carbamazepine, clorazepate (Tranxene, Lundbeck), primidone (Mysoline, Xceld/Valeant), and valproate sodium injection had no effect on vigabatrin plasma concentrations. Co-administration of clonazepam (Klonopin, Roche) had no effect on vigabatrin, but vigabatrin increased the mean peak concentration (C max) of clonazepam by 30% and decreased the time to peak concentration (T max) by 45% in a pharmacokinetic study. Vigabatrin is unlikely to affect the efficacy of steroid oral contraceptives.

**DOSE AND ADMINISTRATION**7,8

Treatment with vigabatrin for refractory complex partial seizures in adults is initiated at 1 g/day, given as 500 mg twice daily with or without meals. The dose may be increased in 500-g increments at weekly intervals up to 3 g/day given as 1,500 mg twice daily. For infantile spasms in children one month to two years of age, therapy is initiated at 50 mg/kg per day with or without meals at two divided doses. The dosage can be titrated upward in increments of 25 to 50 mg/kg per day every three days, to a maximum dose of 150 mg/kg per day (Table 1). Dose adjustments are needed for patients with renal impairment (Table 2). The dose or frequency of administration may need to be adjusted in older patients.

**CONTRAINDICATIONS AND PRECAUTIONS**7,8

The manufacturer has not determined specific contraindications with vigabatrin; however, because of the drug’s association with progressive permanent vision loss, frequent ophthalmologic monitoring is necessary with its use. Vigabatrin should be withdrawn if the patient has not experienced substantial clinical benefit within three months after beginning therapy, or sooner if treatment failure becomes obvious. Patients’ responses and their continued need for vigabatrin should be reassessed periodically.
Therapy should not be discontinued abruptly. Because worsening of depression, suicidal ideation, and abnormal changes in behavior have been reported during therapy, the manufacturer recommends close monitoring.

BOXED WARNING7,8

A black-box warning is included in the prescribing information because vigabatrin can cause vision loss in 30% of infants, children, and adults. In adults, the drug causes permanent bilateral concentric visual field constriction ranging from mild to severe, including tunnel vision, resulting in disability.

Vigabatrin may also cause damage to the central retina and may decrease visual acuity. The onset of vision loss can occur within weeks of initial treatment or sooner, during treatment, and even months or years after therapy.

In infants and children, vigabatrin should be withdrawn if no clinical benefits have resulted within two to four weeks after therapy begins. Because assessing vision loss in younger patients can be difficult, monitoring for visual acuity is required at baseline, no later than four weeks after the initiation of therapy, and at least every three months during therapy.

Vision should also be assessed three to six months after the drug is discontinued. Vision loss resulting from vigabatrin use is not reversible. This medication should not be used in patients with a history of, or with risk factors for, any type of irreversible vision loss, and it should not be used with other drugs that are associated with serious ophthalmic adverse effects.

Because of the potential risk of permanent loss of vision, vigabatrin is available only through a restricted distribution program called SHARE (Support, Help, and Resources for Epilepsy). For details of the program, see “Distribution” on this page.

ADVERSE REACTIONS7,8

In addition to permanent vision loss in adults, most common adverse drug reactions seen with vigabatrin during clinical trials included headache, fatigue, somnolence, dizziness, convulsions, upper respiratory tract infections, nasopharyngitis, nystagmus, tremor, blurred vision, memory impairment, weight gain, arthralgia, abnormal coordination, nausea, and diarrhea. Depression, irritability, anxiety, and insomnia have also been reported.

MONITORING REQUIREMENTS7,8

Lundbeck, the manufacturer, requires patients to undergo ophthalmologic examinations, including visual-field evaluation and dilated indirect ophthalmoscopy of the retina at the baseline examination. This assessment should take place no later than four weeks after therapy begins, at least every three months during treatment, and three to six months after therapy is discontinued. The risk of vision loss increases as the dose increases and may occur at any time during or after treatment. Loss of vision is irreversible and might not be immediately evident to the patient.

The manufacturer does not recommend monitoring plasma concentrations of vigabatrin for optimal therapy. As with the other antiepileptic drugs, a gradual dose reduction is recommended when vigabatrin is discontinued. Clinicians may consider monitoring patients for new-onset or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior.

PREGNANCY REGISTRY

To provide information regarding the effects of exposure to vigabatrin in utero, health care providers are advised to recommend that pregnant patients taking vigabatrin enroll in the North American Antiepileptic Drug Pregnancy Registry. Information is available at the Web site, www.aedpregnancyregistry.org. The phone number is 1-888-233-2334.

DISTRIBUTION7,8

A limited number of specialty pharmacies are allowed to administer the Risk Evaluation and Mitigation Strategy (REMS) to help manage the potential for permanent loss of vision associated with

### Table 1  Total Volumes of Vigabatrin to Be Administered To Infants of Various Weights

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Starting Dose 50 mg/kg per day</th>
<th>Maximum Dose 150 mg/kg per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>1.5 mL b.i.d.</td>
<td>4.5 mL b.i.d.</td>
</tr>
<tr>
<td>4</td>
<td>2.0 mL b.i.d.</td>
<td>6.0 mL b.i.d.</td>
</tr>
<tr>
<td>5</td>
<td>2.5 mL b.i.d.</td>
<td>7.5 mL b.i.d.</td>
</tr>
<tr>
<td>6</td>
<td>3.0 mL b.i.d.</td>
<td>9.0 mL b.i.d.</td>
</tr>
<tr>
<td>7</td>
<td>3.5 mL b.i.d.</td>
<td>10.5 mL b.i.d.</td>
</tr>
<tr>
<td>8</td>
<td>4.0 mL b.i.d.</td>
<td>12.0 mL b.i.d.</td>
</tr>
<tr>
<td>9</td>
<td>4.5 mL b.i.d.</td>
<td>13.5 mL b.i.d.</td>
</tr>
<tr>
<td>10</td>
<td>5.0 mL b.i.d.</td>
<td>15.0 mL b.i.d.</td>
</tr>
<tr>
<td>11</td>
<td>5.5 mL b.i.d.</td>
<td>16.5 mL b.i.d.</td>
</tr>
<tr>
<td>12</td>
<td>6.0 mL b.i.d.</td>
<td>18.0 mL b.i.d.</td>
</tr>
<tr>
<td>13</td>
<td>6.5 mL b.i.d.</td>
<td>19.5 mL b.i.d.</td>
</tr>
<tr>
<td>14</td>
<td>7.0 mL b.i.d.</td>
<td>21.0 mL b.i.d.</td>
</tr>
<tr>
<td>15</td>
<td>7.5 mL b.i.d.</td>
<td>22.5 mL b.i.d.</td>
</tr>
<tr>
<td>16</td>
<td>8.0 mL b.i.d.</td>
<td>24.0 mL b.i.d.</td>
</tr>
</tbody>
</table>

b.i.d. = twice daily; kg = kilograms; mg = milligrams; mL = milliliters.
Data from Sabril (vigabatrin) oral solution7 and oral tablets,8 product information.

### Table 2  Dosing of Vigabatrin in Patients with Renal Impairment

<table>
<thead>
<tr>
<th>Estimated Creatinine Clearance</th>
<th>Dosing Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl &gt; 50 to 80 mL/minute</td>
<td>Dose decreased by 25%</td>
</tr>
<tr>
<td>CrCl &gt; 30 to 50 mL/minute</td>
<td>Dose decreased by 50%</td>
</tr>
<tr>
<td>CrCl &gt; 10 to 50 mL/minute</td>
<td>Dose decreased by 75%</td>
</tr>
</tbody>
</table>

Sabril (vigabatrin) oral solution7 and oral tablets,8 product information.
vigabatrin use. Vigabatrin is available exclusively through SHARE. Patients must be enrolled in the program by their prescribing physicians and must agree to comply with the program’s requirements before they may receive the product. Only physicians registered with SHARE can prescribe vigabatrin, and only a few specialty pharmacies may dispense it. The phone number is 888-45-SHARE.

CONCLUSION

In randomized controlled clinical trials, vigabatrin tablets helped to reduce the frequency of seizures in patients with drug-resistant partial epilepsy. Efficacy was based on the reduction in mean monthly frequency of complex partial seizures and partial seizures with secondary generalization at the end of the study compared with baseline values. More recently, the oral solution of vigabatrin was approved for treating infantile spasms.

A short-term follow-up evaluation of patients revealed side effects associated with its use. Further analysis of longer-term observational studies is required to evaluate how likely visual field defects are to develop and whether such adverse effects are associated with the dose and duration of use. A selective, irreversible enzyme-activated GABA transaminase inhibitor, vigabatrin increases the level of the inhibitory neurotransmitter GABA in the brain and thus reduces seizure activity.

Because of the risk of vision loss, vigabatrin is available only through a restricted distribution program. Several studies are being conducted to evaluate vigabatrin as an adjunctive therapy in patients 10 years of age and older with refractory complex partial seizures, the development of visual lesions, the timing and risk of the development of concentric field loss, the risk of visual acuity deficits, the potential for progression of lesions with continuing therapy, and the potential for progression of vision loss after therapy is discontinued.

REFERENCES