Sabril® (vigabatrin) is an oral antiepileptic drug (AED) approved both as a tablet and powder for oral solution by the U.S. Food and Drug Administration (FDA).\(^1\) SABRIL is indicated as monotherapy for pediatric patients one month to two years of age with infantile spasms (IS) for whom the potential benefits outweigh the potential risk of vision loss and as adjunctive (or add-on) treatment for adults and children ten years of age or older with refractory complex partial seizures (CPS) who have inadequately responded to several alternative treatments and for whom the potential benefits outweigh the risk of vision loss. SABRIL is not indicated as a first line agent for CPS.

SABRIL causes permanent bilateral concentric visual field constriction. Because assessing vision may be difficult in infants and children, the frequency and extent of vision loss in pediatric patients are poorly characterized.\(^1\) In adults, 30% or more of patients can be affected, ranging in severity from mild to severe, including tunnel vision to within 10° of visual fixation, and can result in disability. SABRIL can also damage the central retina and may decrease visual acuity.

The onset of vision loss is unpredictable and can occur soon after starting treatment, at any time during treatment, even after months or years, or possibly after discontinuation. Symptoms of vision loss from SABRIL are unlikely to be recognized by patients or caregivers before it is severe. Vision loss of milder severity may still adversely affect function.

Because of this risk of permanent vision loss, SABRIL approval is accompanied by an FDA-mandated Risk Evaluation and Mitigation Strategy (REMS) and is available only through a restricted distribution program called SHARE (Support, Help And Resources for Epilepsy).

Please see SABRIL Medication Guide, full Prescribing Information including Boxed Warning, and Instructions for Use; go to www.sabril.net, or call toll-free 1-888-45-SHARE (1-888-457-4273).
About Sabril

- SABRIL® (vigabatrin) was the first therapy approved in the U.S. for the treatment of IS, a difficult-to-treat form of epilepsy that primarily affects infants and is characterized by spasms that typically occur in clusters of up to 100 at a time. SABRIL, as add-on therapy, is also an important therapeutic option for patients aged ten and older with refractory CPS who have inadequately responded to several alternative treatments.

- SABRIL was synthesized in 1975 in a deliberate attempt to find a molecule that would increase central nervous system levels of the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA). The precise mechanism of SABRIL's antiseizure effect is unknown, but is believed to be the result of its action as an irreversible inhibitor of gamma-aminobutyric acid transaminase (GABA-T), the enzyme responsible for the metabolism of GABA. This action results in increased levels of GABA in the central nervous system. No direct correlation between plasma concentration and efficacy has been established. The duration of drug effect is presumed to be dependent on the rate of enzyme re-synthesis rather than on the rate of elimination of the drug from the systemic circulation.

Clinical Highlights in the Treatment of Uncontrolled Complex Partial Seizures in Adults Using SABRIL as Add-on Therapy

- Efficacy was demonstrated in two U.S. multicenter, double-blind, placebo-controlled, parallel-group clinical studies as add-on therapy for adult patients with uncontrolled CPS. These studies were not capable by design of demonstrating direct superiority of SABRIL over any other anticonvulsant added to a regimen to which the patient had not adequately responded. Further, in these studies patients had previously been treated with a limited range of anticonvulsants.

- The primary measure of efficacy was the reduction in monthly frequency of complex partial seizures plus partial seizures secondarily generalized at end of study compared to baseline.

- The first study was a randomized, double-blind, placebo-controlled, dose-response study (N=174) consisting of an 8-week baseline period followed by an 18-week treatment period. Patients were randomized to receive placebo or 1, 3, or 6 g/day of SABRIL administered twice daily. During the first 6 weeks following randomization, the dose was titrated upward beginning with 1 g/day and increased by 0.5 g/day on days 1 and 5 of each subsequent week in the 3 g/day and 6 g/day groups, until the assigned dose was reached.

- A second study (N=183 randomized, 182 evaluated for efficacy) was a randomized, double-blind, placebo-controlled, parallel study consisting of an 8-week baseline period and a 16-week treatment period. During the first 4 weeks following randomization, the dose of SABRIL was titrated upward beginning with 1 g/day and increased by 0.5 g/day on a weekly basis to the maintenance dose of 3 g/day.

- The two pivotal clinical trials demonstrated that patients experienced a reduction in monthly complex partial seizures with SABRIL as add-on therapy. In the first study, patients receiving 3 g/day or 6 g/day of SABRIL achieved a reduction in median monthly seizure frequency of 4.8 and 4.0 respectively versus 0.2 in the placebo group. The 3 g/day and the 6 g/day dose groups as add-on therapy were statistically significantly superior to placebo, but the 6 g/day dose was not superior to the 3 g/day dose. A 6 g/day dose has not been shown to confer additional benefit compared to the 3 g/day dose and is associated with increased incidence of adverse events. In the second study, patients receiving 3 g/day of SABRIL achieved a reduction in median monthly seizure frequency of 2.8 versus 1.5 in the placebo group.

- In the first study with SABRIL as add-on therapy, 51 percent of patients in the SABRIL 3 g/day group and 53 percent of patients in the 6 g/day group experienced a ≥ 50 percent reduction in seizure
frequency (responder rate) versus 9 percent in the placebo group. In the second study, the responder rate (at least 50 percent seizure reduction) was 39 percent in patients treated with SABRIL 3 g/day as add-on therapy versus 21 percent in patients in the placebo group.

- The most common adverse reactions in controlled studies in adults >16 years of age (change of ≥5% over placebo) include fatigue, somnolence, nystagmus, tremor, vision blurred, memory impairment, weight gain, arthralgia, abnormal coordination, and confusional state.

Clinical Highlights in the Treatment of Uncontrolled Complex Partial Seizures in Pediatric Patients 10 to 16 Years of Age Using SABRIL as Add-on Therapy

- SABRIL was studied in three double-blind, placebo-controlled, parallel-group, adjunctive-treatment studies in 269 patients who received SABRIL and 104 patients who received placebo. Patients had uncontrolled complex partial seizures with or without secondary generalization.

- No individual study was considered adequately powered to determine efficacy in pediatric patients age 10 years and above. The data from all three pediatric studies were pooled and used in a pharmacometric bridging analysis using weight-normalized doses to establish efficacy and determine appropriate dosing.

- The study period included a 6 to 10 week baseline phase and a 14 to 17 week treatment phase (composed of a titration and maintenance period).

- The pharmacometric bridging approach consisted of defining a weight-normalized dose-response, and showing that a similar dose-response relationship exists between pediatric patients and adult patients when SABRIL was given as adjunctive therapy for complex partial seizures. Dosing recommendations in pediatric patients 10 to 16 years of age were derived from simulations utilizing these pharmacometric dose-response analyses.

- The most common adverse events in controlled studies in pediatrics 10 to 16 years of age (change of ≥5% over placebo) include increased weight, upper respiratory tract infection, tremor, fatigue, aggression and diplopia.

Clinical Highlights in the Treatment of Infantile Spasms

- Efficacy of SABRIL as monotherapy was demonstrated for IS in two multicenter controlled studies. Both studies were similar in terms of disease characteristics and prior treatments of patients and all enrolled infants had a confirmed diagnosis of IS.

- The first study (N=221) was a multicenter, randomized, low-dose, high-dose, parallel group, partially-blinded (caregivers blinded to arm but not to dose: EEG-reader blinded but investigators not blinded) study involving infants less than 2 years of age with new onset IS. Patients with both symptomatic and cryptogenic etiologies were studied. The study was comprised of two phases. The first phase was a 14 to 21 day partially-blind phase in which patients were randomized to receive low-dose (18 - 36 mg/kg/day) or high-dose (100 – 148 mg/kg/day) SABRIL. SABRIL was titrated over 7 days, followed by a constant dose for 7 days. If the patient became spasm-free on or before day 14, another 7 days of constant dose was administered.

  - The primary efficacy endpoint was the proportion of patients who were spasm free for 7 consecutive days beginning within the first 14 days of SABRIL therapy. Patients considered spasm-free had to remain free of spasms (evaluated according to caregiver response to direct questioning regarding spasm frequency) and had to have no indication of spasms or hypsarrhythmia during 8 hours of CCTV EEG recording (including at least one sleep-wake-sleep cycle) performed within 3 days of the seventh day of spasm freedom and interpreted by a blinded EEG reader.

  - Sixteen percent of infants (17/107) in the high-dose group achieved spasm freedom versus 7
percent of infants (8/114) in the low-dose group. The difference between dosing groups was statistically significant.

- The second study (N=40) was a multicenter, randomized, double-blind, placebo-controlled, parallel group study consisting of a pretreatment (baseline) period of 2–3 days, followed by a 5-day double-blind treatment phase during which patients were treated with SABRIL (n=20) (initial dose of 50 mg/kg/day with titration allowed to 150 mg/kg/day) or placebo (n=20).
  - The primary efficacy endpoint was the average percent change in daily spasm frequency, assessed during a predefined and consistent 2-hour window of evaluation, comparing baseline to the final 2-days of the 5-day double-blind treatment phase.
  - No statistically significant differences were observed in the average frequency of spasms using the 2-hour evaluation window. However, a post-hoc alternative efficacy analysis, using a 24-hour clinical evaluation window, found a statistically significant difference in the overall percentage of reductions in spasms between the SABRIL group (68.9 percent) and the placebo group (17 percent).

- In the first study, a dose response study of low-dose (18-36 mg/kg/day) versus high-dose (100-148 mg/kg/day) vigabatrin, no clear correlation between dose and incidence of adverse events was observed.

- In the second study, a randomized, placebo-controlled IS study with a 5 day double-blind treatment phase (n=40), the adverse events reported by >5% of patients receiving SABRIL and that occurred more frequently than in placebo patients, were somnolence (SABRIL 45%, placebo 30%), bronchitis (SABRIL 30%, placebo 15%), ear infection (SABRIL 10%, placebo 5%), and acute otitis media (SABRIL 10%, placebo 0%).

- In patients with infantile spasms, the adverse reactions most commonly associated with SABRIL treatment discontinuation in ≥1% of patients were infections, status epilepticus, developmental coordination disorder, dystonia, hypotonia, hypertonia, weight increased, and insomnia.

**Sabril-induced Permanent Vision Loss**

- SABRIL causes permanent bilateral concentric visual field constriction. Because assessing vision may be difficult in infants and children, the frequency and extent of vision loss in pediatric patients are poorly characterized. In adults, 30% or more of patients can be affected, ranging in severity from mild to severe, including tunnel vision to within 10° of visual fixation, and can result in disability. SABRIL can also damage the central retina and may decrease visual acuity.

- The onset of vision loss is unpredictable and can occur soon after starting treatment, at any time during treatment, even after months or years, or possibly after discontinuation. Symptoms of vision loss from SABRIL are unlikely to be recognized by patients or caregivers before it is severe. Vision loss of milder severity may still adversely affect function.

- Unless a patient is formally exempted from periodic ophthalmologic assessment as documented in the SHARE Program, vision should be assessed at baseline (no later than 4 weeks after starting SABRIL), every 3 months during therapy, and at 3 to 6 months after discontinuing therapy. Once detected, vision loss is not reversible. Even with frequent monitoring, some patients will develop severe vision loss. Consider drug discontinuation, balancing benefit and risk, if vision loss is documented.

- Because of the risk of permanent vision loss, withdraw SABRIL from patients with refractory complex partial seizures who fail to show substantial clinical benefit within 3 months of initiation, and from patients with infantile spasms who fail to show substantial clinical benefit within 2 to 4 weeks of initiation, or sooner, if treatment failure becomes obvious. Periodically reassess patient response and continued need for SABRIL.

- Do not use SABRIL in patients with, or at high risk of, other types of irreversible vision loss,

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or, with other drugs associated with serious adverse ophthalmic effects, unless the benefits clearly outweigh the risks. The interaction in these situations has not been well characterized, but is likely adverse.

- Use the lowest dose and shortest exposure to SABRIL that is consistent with clinical objectives.
- Because of the risk of permanent vision loss, SABRIL is available only through a restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS) called the SHARE Program.

Safety and Tolerability Highlights¹

- Abnormal MRI signal changes characterized by increased T2 signal and restricted diffusion in a symmetric pattern involving the thalamus, basal ganglia, brain stem, and cerebellum have been observed in some infants treated with vigabatrin for infantile spasms.
- In a retrospective epidemiologic study in infants with IS (N=205), the prevalence of these changes was 22% in vigabatrin treated patients versus 4% in patients treated with other therapies.
  - In the study above, in post marketing experience, and in published literature reports, these changes generally resolved with discontinuation of treatment. In a few patients, the lesion resolved despite continued use. It has been reported that some infants exhibited coincident motor abnormalities, but no causal relationship has been established and the potential for long-term clinical sequelae has not been adequately studied.
  - The specific pattern of signal changes observed in IS patients was not observed in older pediatric and adult patients treated with SABRIL for refractory CPS. In a blinded review of MRI images obtained in prospective clinical trials in patients with refractory CPS 3 years and older (N=656), no difference was observed in anatomic distribution or prevalence of MRI signal changes between SABRIL treated and placebo treated patients.
- For adults treated with SABRIL, routine MRI surveillance is unnecessary as there is no evidence that vigabatrin causes MRI changes in this population.
- AEDs, including SABRIL, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. The risk of suicidal thoughts or behavior in patients receiving SABRIL was generally consistent among other AEDs studied.
- Although phenytoin dose adjustments are not routinely required, dose adjustment of phenytoin should be considered if clinically indicated, since SABRIL may cause a moderate reduction in total phenytoin plasma levels.
- SABRIL may moderately increase the C_{max} of clonazepam resulting in an increase of clonazepam-associated adverse reactions.

For additional safety information please see Important Safety Information on the next page.

Lundbeck SHARE Program

Lundbeck is committed to help ensure that its products are appropriately available to patients in need. SHARE (Support, Help And Resources for Epilepsy), the company’s comprehensive patient and physician support program, is designed to support use of SABRIL. The FDA-mandated SABRIL Risk Evaluation and Mitigation Strategy (REMS) is administered through SHARE and includes measures such as restricted distribution through a limited number of specialty pharmacies, mandatory benefit-risk assessments and required vision testing, to manage the risk of permanent vision loss associated with SABRIL therapy. Additionally, through SHARE, Lundbeck offers programs to help facilitate access to SABRIL for those who may potentially benefit from treatment. These programs include a starter prescription program, a reimbursement support program and additional assistance programs for eligible patients and where legally permissible. The SHARE Call Center is also available to help patients and their caregivers and physicians fully understand and navigate the SABRIL prescribing process step-by-step. To learn more about SHARE, please visit www.sabril.net.
SABRIL® (vigabatrin) tablets, for oral use
SABRIL® (vigabatrin) powder for oral solution

Use

SABRIL (vigabatrin) is a prescription medicine used with other treatments in adults and children 10 years of age and older with refractory complex partial seizures (CPS), who have not responded well enough to several other treatments, and if the possible benefits outweigh the risk of vision loss. SABRIL should not be the first medicine used to treat CPS.

SABRIL (vigabatrin) is a prescription medicine used in babies, 1 month to 2 years old, with infantile spasms (IS), if the possible benefits outweigh the possible risk of vision loss.

Important Safety Information

WARNING: VISION LOSS
See Medication Guide and full Prescribing Information for complete information

In all people who take SABRIL:

- You are at risk for vision loss with any amount of SABRIL
- Your risk of vision loss may be higher the more SABRIL you take daily and the longer you take it
- It is not possible for your healthcare provider to know when vision loss will happen. It could happen soon after starting SABRIL or any time during treatment. It may even happen after treatment has stopped.

- Because SABRIL might cause vision loss, it is available to healthcare providers and patients only under a special program called the Support, Help And Resources for Epilepsy (SHARE) Program. Your healthcare provider will explain the details of the SHARE Program to you.

- SABRIL can permanently damage the vision of anyone who takes it. The most noticeable loss is in the ability to see to the side when looking straight ahead (peripheral vision). If this happens, it will not get better. People who take SABRIL do not lose all of their vision, but some people can have severe loss and may only be able to see things straight in front of them (sometimes called “tunnel vision”), and they may also have blurry vision.

- Tell your healthcare provider right away if you (or your child): might not be seeing as well as before starting SABRIL; start to trip, bump into things, or are more clumsy than usual; are surprised by people or things coming in front of you that seem to come out of nowhere; or if your baby is acting differently than normal. These changes can mean that vision damage has occurred.

- Your healthcare provider will test your (or your child's) vision before or within 4 weeks after starting SABRIL, and at least every 3 months during treatment until SABRIL is stopped. Vision should also be tested about 3 to 6 months after SABRIL is stopped. You (or your child) may not be able to be tested in certain situations. It is difficult to test vision in babies, but to the extent possible, all babies should have their vision tested. Your healthcare provider will determine if testing can be done. Regular vision testing is important because damage can happen before any changes are noticed.

- Vision tests cannot prevent the vision damage that can happen with SABRIL, but they do allow SABRIL to be stopped if vision has gotten worse, which usually will lessen further damage. Even these regular vision tests may not show vision damage before it is serious and
permanent. Parents, caregivers, and healthcare providers may not recognize the symptoms, or find vision loss in babies, until it is severe.

- If vision tests are not done regularly, your healthcare provider may stop prescribing SABRIL for you (or your child). Some people are not able to complete vision testing. If vision testing cannot be done, your healthcare provider may continue prescribing SABRIL, but will not be able to watch for any vision loss.

- Brain pictures taken by magnetic resonance imaging (MRI) show changes in some babies after they are given SABRIL. It is not known if these changes are harmful.

- Like other antiepileptic drugs, SABRIL may cause suicidal thoughts and actions in some people. Call a healthcare provider right away if you (or your child) have any symptoms, especially sudden changes in mood, behaviors, thoughts or feelings, and especially if they are new, worse, or worry you.

- Do not stop SABRIL without first talking to a healthcare provider. Stopping SABRIL suddenly can cause seizures that will not stop.

- SABRIL can cause serious side effects such as low red blood cell counts, sleepiness and tiredness, nerve problems, weight gain, and swelling. Because SABRIL causes sleepiness and tiredness, do not drive, operate machinery, or perform hazardous tasks, unless it is decided that these things can be done safely. SABRIL may make certain types of seizures worse. Tell your healthcare provider right away if seizures get worse.

- Before starting SABRIL, tell your doctor about all of your (or your child’s) medical conditions including depression, mood problems, suicidal thoughts or behavior, any allergic reaction to SABRIL, vision problems, kidney problems, low red blood cell counts, and any nervous or mental illness. Tell your doctor about all the medicines you (or your child) take.

- If you are breastfeeding or plan to breastfeed, SABRIL can pass into breast milk and may harm your baby. If you are pregnant or plan to become pregnant, it is not known if SABRIL will harm your unborn baby. You and your healthcare provider will have to decide if you should take SABRIL while you are pregnant.

- The most common side effects of SABRIL in adults include: problems walking or feeling uncoordinated, feeling dizzy, shaking (tremor), joint pain, memory problems and not thinking clearly, eye problems like blurry vision, double vision, and eye movements that cannot be controlled. The most common side effects of SABRIL in children 10 to 16 years of age include weight gain, upper respiratory tract infection, tiredness, and aggression. Also expect side effects like those seen in adults.

- The most common side effects of SABRIL in babies include: sleepiness—some babies may have a harder time suckling and feeding or may be irritable, swelling in the bronchial tubes (bronchitis), ear infection, and irritability.

- Tell your healthcare provider if you or your child have any side effect that bothers you or that does not go away. These are not all of the possible side effects of SABRIL. For more information, ask your healthcare provider or pharmacist.

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You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.
**Sources**


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