# Vigabatrin Products

**Policy #** 00244
Original Effective Date: 12/16/2009
Current Effective Date: 03/13/2023

*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

*Note: Repository corticotropin Injection (ACTH Gel, H.P. Acthar Gel) is addressed separately in medical policy 00230.*

# When Services May Be Eligible for Coverage

*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider brand or generic vigabatrin (Sabril®, Vigadrone™)‡ for the treatment of infantile spasms or refractory complex partial seizures to be **eligible for coverage.****

**Infantile Spasms**

Patient Selection Criteria

Coverage eligibility for brand or generic vigabatrin (Sabril, Vigadrone) for the treatment of infantile spasms (IS) will be considered when all of the following criteria are met:

- Patient has a diagnosis of infantile spasms; AND
- Patient is 1 month to 2 years of age; AND
- Vigabatrin is used as monotherapy.

**Refractory Complex Partial Seizures**

Patient Selection Criteria

Coverage eligibility for brand or generic vigabatrin (Sabril, Vigadrone) for the treatment of refractory complex partial seizures will be considered when all of the following criteria are met:

- Patient has a diagnosis of refractory complex partial seizures (CPS); AND
- Patient is greater than or equal to 2 years of age; AND

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- Vigabatrin is used as adjunctive therapy in patients who have inadequately responded to alternative treatments and not as a first line agent for CPS.

# When Services Are Considered Investigational

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers the use of brand or generic vigabatrin (Sabril, Vigadrone) when patient selection criteria are not met to be **investigational.***

# Background/Overview

**About vigabatrin Tablets and Oral Solution**

Vigabatrin is an oral antiepileptic drug that is available in two formulations—500 mg tablets and 500 mg packets of powder for oral solution. There are generics available for both formulations including Vigadrone, which is a generic version of the 500 mg powder packets marketed under a brand name. All approved vigabatrin products are indicated as add-on therapy for patients greater than or equal to 2 years of age with refractory complex partial seizures (CPS) and for infants with infantile spasms (IS). The precise mechanism of vigabatrin'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 the inhibitory neurotransmitter 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.

Because of the risk of permanent vision loss, vigabatrin is available only through a special restricted distribution program called the Vigabatrin REMS program. Only prescribers and pharmacies registered with the Vigabatrin REMS program may prescribe and distribute vigabatrin. In addition, vigabatrin may be dispensed only to patients who are authorized to receive vigabatrin.

**Infantile Spasms**

Infantile spasms is a difficult-to-treat epilepsy syndrome that usually strikes infants between three to six months old. An estimated 8,500 infants in the U.S. have been diagnosed with IS, and each

year approximately 2,500 new cases of IS are reported in the U.S. Sabril may not be appropriate for use in all patients with IS.

**Complex Partial Seizures**
Of the three million Americans affected by epilepsy, approximately 35 percent have CPS, the single largest seizure type which originates from a single region of the brain and can cause impaired consciousness. Despite the availability of many antiepileptic drugs, approximately 30 to 36 percent of adults with CPS continue to have seizures. Vigabatrin provides an add-on treatment option for CPS patients greater than or equal to 2 years of age who have not responded to several alternative treatments and are considered 'refractory' to treatment. Given the potential benefit compared to the risk of permanent vision loss, it is expected that only a small percentage of refractory CPS patients will initiate and maintain treatment with vigabatrin as add-on therapy.

# FDA or Other Governmental Regulatory Approval

**U.S. Food and Drug Administration (FDA)**
On August 21, 2009, the FDA approved vigabatrin (Sabril) oral solution and tablets for treatment of IS and refractory CPS in patients who have inadequately responded to other anti-epilepsy drugs (AEDs). Sabril was the first therapy approved for the treatment of IS. In October of 2013, the age for treatment of refractory CPS was changed to greater than or equal to 10 years of age. In February of 2020, the age for refractory CPS was again expanded to include patients greater than or equal to 2 years of age.

# Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

**Infantile Spasms**
The effectiveness of vigabatrin as monotherapy was established 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.

Study 1 (N=221) was a multicenter, randomized, low-dose high-dose, parallel group, partially-blinded (caregivers knew the actual dose but not whether their child was classified as low or high dose; EEG reader was blinded but investigators were not blinded) study to evaluate the safety and efficacy of vigabatrin in patients <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 either low-dose (18-36 mg/kg/day) or high-dose (100-148 mg/kg/day) vigabatrin. Study drug was titrated over seven days, followed by a constant dose for seven days. If the patient became spasm-free on or before day 14, another seven days of constant dose was administered. The primary efficacy endpoint of this study was the proportion of patients who were spasm-free for seven consecutive days beginning within the first 14 days of vigabatrin therapy. Patients considered spasm-free were defined as those patients who remained free of spasms (evaluated according to caregiver response to direct questioning regarding spasm frequency) and who had no indication of spasms or hypsarrhythmia during eight hours of CCTV EEG recording (including at least one sleep-wake-sleep cycle) performed within three days of the seventh day of spasm freedom and interpreted by a blinded EEG reader. Seventeen patients in the high dose group achieved spasm freedom compared with eight patients in the low dose group.

Study 2 (N=40) was a multicenter, randomized, double-blind, placebo-controlled, parallel group study consisting of a pre-treatment (baseline) period of two to three days, followed by a five-day double-blind treatment phase during which patients were treated with vigabatrin (initial dose of 50 mg/kg/day with titration allowed to 150 mg/kg/day) or placebo. The primary efficacy endpoint in this study was the average percent change in daily spasm frequency, assessed during a pre-defined and consistent two-hour window of evaluation, comparing baseline to the final two days of the five-day double-blind treatment phase. No statistically significant differences were observed in the average frequency of spasms using the two-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 vigabatrin group (68.9%) and the placebo group (17.0%) (p=0.030).

**Complex Partial Seizures in Adults**

The effectiveness of vigabatrin as adjunctive therapy in adult patients with CPS was established in two U.S. multicenter, double-blind, placebo-controlled, parallel-group clinical studies. A total of 357 adults (age 18 to 60 years) with CPS, with or without secondary generalization were enrolled

(Studies 1 and 2). Patients were required to be on an adequate and stable dose of an anticonvulsant and have a history of failure on an adequate regimen of carbamazepine or phenytoin. Patients had a history of about eight seizures per month (median) for about 20 years (median) prior to entrance into the study. These studies were not capable by design of demonstrating direct superiority of vigabatrin 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 patient's reduction in mean monthly frequency of complex partial seizures plus partial seizures secondarily generalized at end of study compared to baseline. Study 1 (N=174) was a randomized, double-blind, placebo-controlled, dose-response study 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 vigabatrin administered twice daily. During the first six weeks following randomization, the dose was titrated upward beginning with 1 g/day and increasing 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. The 3 g/day and 6 g/day dose groups were statistically significantly superior to placebo, but the 6 g/day dose was not superior to the three g/day dose.

Study 2 (N=183 randomized, 182 evaluated for efficacy) was a randomized, double blind, placebo-controlled, parallel study consisting of an eight-week baseline period and a 16-week treatment period. During the first four weeks following randomization, the dose of vigabatrin 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. Vigabatrin 3 g/day was statistically significantly superior to placebo in reducing seizure frequency.

**Complex Partial Seizures in Patients 3 to 16 Years of Age**

Vigabatrin was studied in three double-blind, placebo-controlled, parallel-group studies in 269 patients who received Sabril and 104 patients who received placebo. No individual study was considered adequately powered to determine efficacy in pediatric patients age 3 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. All three studies were randomized, double-blind, placebo-controlled, parallel-group, adjunctive-treatment studies in patients aged 3-16 years with uncontrolled complex partial seizures with or without secondary generalization. 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 vigabatrin was given as adjunctive therapy for complex partial seizures. Dosing recommendations in pediatric patients 2 to 16 years of age were derived from simulations utilizing these pharmacometric dose-response analyses.

# References

1. Sabril (vigabatrin) Full Prescribing Information. Updated May 2020.
2. Kwan P, Brodie MJ. Early identification of refractory epilepsy. New England Journal of Medicine. February 3, 2000;342:314-319.
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5. Murro, Anthony M. EMedicine.com. Complex Partial Seizures. http://www.emedicine.com/Neuro/topic74.htm
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7. National Institute of Neurological Disorders and Stroke. NINDS Infantile Spasms Information Page. Available at: http://www.ninds.nih.gov/disorders/infantilespasms/infantilespasms.htm?css=print.
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9. Vermes K. REMS for Sabril Modified. Pharmacy Times. June 2016.
10. Vigadrone (vigabatrin) Full Prescribing Information. Updated Feb 2020.

# Policy History

Original Effective Date: 12/16/2009
Current Effective Date: 03/13/2023
12/04/2009 Medical Policy Committee approval
12/16/2009 Medical Policy Implementation Committee approval. New policy.
12/01/2010 Medical Policy Committee approval

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| 12/15/2010 | Medical Policy Implementation Committee approval. No change to coverage. |
| 12/08/2011 | Medical Policy Committee approval |
| 12/21/2011 | Medical Policy Implementation Committee approval. No change to coverage. |
| 12/06/2012 | Medical Policy Committee approval |
| 12/19/2012 | Medical Policy Implementation Committee approval. No change to coverage. |
| 12/12/2013 | Medical Policy Committee approval |
| 12/18/2013 | Medical Policy Implementation Committee approval. No change to coverage. FDA has combined the indications for both formulations of Sabril. Also extended the age for complex partial seizures to match new FDA expanded indication. |
| 12/04/2014 | Medical Policy Committee approval |
| 12/17/2014 | Medical Policy Implementation Committee approval. No change to coverage. |
| 12/03/2015 | Medical Policy Committee approval |
| 12/16/2015 | Medical Policy Implementation Committee approval. No change to coverage. |
| 12/01/2016 | Medical Policy Committee approval |
| 12/21/2016 | Medical Policy Implementation Committee approval. No change to coverage. |
| 01/01/2017 | Coding update: Removing ICD-9 Diagnosis Codes |
| 12/07/2017 | Medical Policy Committee approval |
| 12/20/2017 | Medical Policy Implementation Committee approval. No change to coverage. |
| 02/07/2019 | Medical Policy Committee approval |
| 02/20/2019 | Medical Policy Implementation Committee approval. Title changed from "vigabatrin (Sabril)" to "Vigabatrin Products". Added generic formulation and updated background information to reflect the generic availability and changes to the REMS program. |
| 02/06/2020 | Medical Policy Committee approval |
| 02/12/2020 | Medical Policy Implementation Committee approval. No change to coverage. |
| 02/04/2021 | Medical Policy Committee review |
| 02/10/2021 | Medical Policy Implementation Committee approval. Updated criteria to extend the age for complex partial seizures to $\geq$2 years to match the expanded FDA indication. |
| 02/03/2022 | Medical Policy Committee review |
| 02/09/2022 | Medical Policy Implementation Committee approval. No change to coverage. |
| 02/02/2023 | Medical Policy Committee review |
| 02/08/2023 | Medical Policy Implementation Committee approval. No change to coverage. |

Next Scheduled Review Date: 02/2024

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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

**NOTICE:** If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

**NOTICE:** Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.