| Subject: Sabril (vigabatrin) | Original Effective Date: 4/27/11 |
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## DISCLAIMER

*This Medical Policy is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina Clinical Policy (MCP) document and provide the directive for all Medicare members.*

## SUMMARY OF EVIDENCE/POSITION

This policy addresses the coverage of **Sabril (vigabatrin)** for the treatment of **infantile spasm and refractory complex partial seizures (CPS)** when appropriate criteria are met.

- Sabril is the first drug to receive FDA approval for the treatment of IS as monotherapy.[e] Vigabatrin may reduce the number of spasms in infants with infantile spasms, however safety concerns may outweigh potential benefit in some cases.

- Vigabatrin (Sabril) is a selective, irreversible, inhibitor of gamma-aminobutyric acid transaminase (GABA-T) the enzyme responsible for the metabolism of the inhibitory neurotransmitter GABA. The goal of vigabatrin is to enhance GABA function in the CNS.

- The precise mechanism of vigabatrin's antiseizure effect is unknown. Its antiseizure effect is believed to be the result of its effect on GABA levels. Vigabatrin therapy results in increased levels of free and total GABA in the CNS.[a] By increasing brain concentrations of this inhibitory neurotransmitter the drug appears to decrease propagation of abnormal hypersynchronous discharges, thereby reducing seizure activity. This binding of GABA by viagatrin is irreversible.

- While vigabatrin has demonstrated efficacy in a refractory seizure population the side-effect profile of vigabatrin remains a concern, particularly in the adult patient. Visual changes appear to be irreversible in infants, children and adults. The potential for development of visual field loss which is not reversible and which may continue to worsen despite discontinuation of therapy should limit the use of vigabatrin. A complete discussion of the potential for visual field loss should occur with the patient prior to therapy. The use of vigabatrin should be restricted to refractory patients under the care of an epileptologist.

- There have been no specific patient characteristics identified so far to indicate which individuals might be more or less susceptible to development of the defects. The onset of vision loss from Sabril is unpredictable, and can occur within weeks of starting treatment or sooner, or at any time during treatment, even after months or years.

- Vigabatrin causes permanent vision loss in infants, children, and adults. Due to the risk of vision loss and because vigabatrin, provides an observable symptomatic benefit when it is effective, the patient who fails to show substantial

clinical benefit within a short period of time after initiation of treatment (2 to 4 weeks for infantile spasms; less than 3 months for refractory complex partial seizures), should be withdrawn from therapy. If in the clinical judgment of the prescriber evidence of treatment failure becomes obvious earlier in treatment, vigabatrin should be discontinued at that time.

**CLASSIFICATION: Neurological Agents; Anticonvulsants**

## FDA INDICATIONS

**Sabril (vigabatrin)** is indicated for the following:

- **Infantile Spasms** Vigabatrin (Sabril) is indicated as monotherapy for pediatric patients 1 month to 2 years of age with infantile spasms (IS) for whom the potential benefits outweigh the potential risk of vision loss.

- **Refractory Complex Partial Seizures (CPS)** Sabril is indicated as adjunctive therapy for **adult** patients 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 complex partial seizures.

**Available as:** Film-Coated Tablets: 500mg, AND Powder for Oral Solution: 500mg packets of granular powder -
500mg Powder for Solution (vigabatrin powder for oral solution for the treatment of infantile spasms) -
500mg Tablet (vigabatrin tablets as adjunctive therapy in the treatment of adults with refractory complex partial seizures) -

**FDA Approved:** August 21, 2009

- August 2009: The FDA approved vigabatrin powder for oral solution for the treatment of infantile spasms and vigabatrin tablets as adjunctive therapy in the treatment of adults with refractory complex partial seizures.
- October 2013: Vigabatrin gained FDA-approval for the treatment of pediatric patients >= 10 years of age with refractory complex partial seizures.

**BLACK BOX WARNINGS:** Vigabatrin causes progressive and permanent bilateral concentric visual field constriction in a high percentage of patients. In some cases, vigabatrin may also reduce visual acuity. Risk increases with total dose and duration of use, but no exposure to vigabatrin is known that is free of risk of vision loss. Risk of new and worsening vision loss continues as long as vigabatrin is used, and possibly after discontinuing vigabatrin. Periodic vision testing is required for patients receiving vigabatrin therapy. However, this assessment cannot always prevent vision damage. Vigabatrin should not be used concomitantly with other drugs associated with adverse ophthalmic effects or in patients at high risk for other types of irreversible vision damage. Vigabatrin can cause permanent vision loss. Vigabatrin is only available through a restricted program called the SHARE Program.

## RECOMMENDATIONS/COVERAGE CRITERIA

**Sabril (vigabatrin)** may be authorized for members who meet **ALL** of the following criteria **[ALL]**

**1. Prescriber specialty [ONE]**

- ❒ Prescribed by, or in consultation with, a board-certified pediatric neurologist, pediatric epileptologist, or physician experienced in the management of infantile spasms
- ❒ Prescribing physician is registered with SHARE (special restricted distribution plan)

**2. Diagnosis/Indication [ONE: A OR B]**
Clinical documented diagnosis of (*includes clinical notes from the member's medical records including any applicable labs and/or tests, supporting the diagnosis*):

- ❒ **Infantile Spasms [ALL]**
  - ❍ Diagnosis of infantile spasms (West Syndrome) confirmed by the presence of hypsarrthymia upon an EEG
    - ➢ *Most affected patients have an interictal EEG pattern known as hypsarrhythmia* (h*ypsarrthymia is an abnormal chaotic brain wave pattern). In the 2010 consensus report, this EEG pattern was identified as a defining feature of IS.*[7]
  - ❍ Documentation for patients with an atypical clinical presentation or lack of hypsarrhythmia on EEG that other cause of the patient's spasms have been excluded, including (but not limited to): [AS APPLICABLE]
    - o Epileptic spasms
      - ➢ *Spasms can involve the muscles of the neck, trunk, and extremities. Spasms are symmetric contractions of flexor or extensor axial or limb muscles. They vary in pattern, intensity, duration and extent. Most spasms occur in clusters of two to more than 100 over one to several minutes.*[7]
    - o Neuroimaging studies (i.e. CT scan, MRI)
      - ➢ *MRI is recommended for all patients with IS. Perform magnetic resonance imaging (MRI) to help determine etiology of spasms. Approximately 70 percent of patients will have an established etiology after clinical evaluation, EEG, and MRI.*
      - ➢ *Neuroimaging studies should be performed in all patients with IS to identify lesions associated with the disorder, as this may influence treatment decisions.*[7]
- ❒ **Refractory Complex Partial Seizures (CPS)**
  - ❍ Diagnosis of refractory complex partial seizures

**3. Age/Gender/Other restrictions [ALL]**

- ❒ Member meets the indicated age for diagnosis:[a] [ONE]
  - ❍ Infantile Spasms: 1 month to 2 years of age [< 24 months]
    - ➢ *The safety and efficacy of vigabatrin has not been established in patients younger than 16 years of age with complex partial seizure; however, it is indicated as monotherapy for children 1 month to 2 years of age with infantile spasms.*[a]

- ❍ Refractory complex partial seizures (CPS): 10 years of age or older

❒ **Baseline vision assessments.** Documentation of ONE (1) of the following: [ONE]

- ❍ Baseline vision assessed by an ophthalmologist (within 90 days of starting therapy) OR no later than 4 weeks after therapy initiation. Documentation required.
  **NOTE:** For infants, vision must be tested to the extent possible depending on the age of the child.

- ❍ Exempt from vision assessments in the SHARE program. SHARE Program vision assessment exemptions: [ONE]
  - o Blindness
  - o General neurological and/or mental condition permanently precludes the need for visual assessment
  - o General neurological condition temporarily precludes the ability to assess visual function.
  - o Medical condition prevents visual assessment being performed safely

**4. Step/Conservative Therapy/Other condition Requirements [ALL]**

❒ Infantile Spasms: For use as **monotherapy** in the treatment of infantile spasms
- ➢ *Sabril (vigabatrin) is indicated as monotherapy for pediatric patients 1 month to 2 years of age with infantile spasms for whom the potential benefits outweigh the potential risk of vision loss.*[a]

❒ Refractory complex partial seizures (CPS): [ALL]

- ❍ Prescribed for use as **adjunctive therapy**: Documentation of concurrent therapy for CPS required.

- ❍ An inadequate response, intolerance, or contraindication to a trial of at least **TWO (2) alternative first-line agents** (i.e. carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, valproic acid; divalproex sodium, clobazam, gabapentin, topiramate). Documentation required.
  - ➢ *Sabril (vigabatrin) is **not** indicated as a first-line agent for CPS.*

❒ Risk of developing permanent vision loss outweighs the potential benefits of the drug. Documentation of acknowledgment from Prescriber.
- ➢ *For all indications, the potential benefits of the drug must outweigh the potential risk for developing permanent vision loss.*[a-e]

❒ Baseline eye examination by an ophthalmologist: Assessment should include visual activity and should be assessed to the extent possible depending on the age of the child at baseline **prior** to start of therapy and at least every 3 months during therapy, and about 3 to 6 months after discontinuation of therapy with vigabatrin.
**Exception to vision assessment:** Member with pre-existing blindness

**5. Contraindications/Exclusions/Discontinuations**

There are no contraindications listed in the manufacturer's labeling.[a]
Authorization will <u>not</u> be granted if ANY of the following conditions apply [ANY]

❒ Non-FDA approved indications
❒ Hypersensitivity to vigabatrin
❒ High risk of, other types of irreversible vision loss or with other drugs associated with serious adverse ophthalmic effects, such as retinopathy or glaucoma unless the benefits clearly outweigh the risks

**6. Labs/Reports/Documentation required [ALL]**

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit medical records and specific labs, chart notes, and documentation as indicated in the criteria above. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP is included.

**NOTE:** Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

## CONTINUATION OF THERAPY

**Sabril (vigabatrin)** may be authorized for continuation of therapy if meet **ALL** of the following criteria are met: **[ALL]**

Vigabatrin causes permanent vision loss in infants, children, and adults. Due to the risk of vision loss and because vigabatrin, provides an observable symptomatic benefit when it is effective, the patient who fails to show substantial clinical benefit within a short period of time after initiation of treatment (2 to 4 weeks for infantile spasms; less than 3 months for refractory complex partial seizures), should be withdrawn from therapy. If in the clinical judgment of the prescriber evidence of treatment failure becomes obvious earlier in treatment, vigabatrin should be discontinued at that time.[a-e]

### 1. Initial Coverage Criteria

- ❑ Member currently meets ALL initial coverage criteria

- ❒ Prescribed by, or in consultation with, a board-certified pediatric neurologist, pediatric epileptologist, or physician experienced in the management of infantile spasms.
  - ➢ *According to a report of the American Academy of Neurology and the Child Neurology Society (2004) on the treatment of IS, ACTH is effective for the short-term treatment of IS and the resolution of hypsarrhythmia; however, there is insufficient evidence to recommend optimum dosage and duration of treatment. Therefore, provisions for exceptional cases to extend Acthar therapy, must be upon a request from pediatric epilepsy specialist and forward to a Molina Medical Director for review.*

### 2. Compliance [ALL]

- ❒ Vision assessed **every 3 months** by an ophthalmic professional and assessment should include visual acuity and visual field whenever possible. If vision testing is not possible, treatment may continue according to clinical judgment with appropriate patient counseling and documentation of the inability to test vision.

  **NOTE:** Unless a member is formally *exempted* from periodic ophthalmologic assessment as documented in the SHARE program, vision should be assessed to the extent possible at baseline (no later than 4 weeks after starting Sabril) and at least every 3 months during therapy. Documentation required.

  - ➢ *Use of vigabatrin involves a continuous analysis of its risks and benefits. This approach requires cooperation among the patient's neurologist, ophthalmologist and member/caregiver.*
  - ➢ *Because of the risk of vision loss, Sabril should be withdrawn from patients with infantile spasms who fail to show substantial clinical benefit within two to four weeks of initiation, or sooner if treatment failure becomes obvious. Patient response to and continued need for Sabril should be periodically reassessed.*

### 3. Labs/Reports/Documentation required [ALL APPLICABLE]

- ❒ Member has experienced an objective response to therapy (i.e. reduction in the occurrence of seizures or substantial clinical benefit). Documentation required.

- ❒ Submission of progress notes with taper schedule intended if continuation of treatment is authorized
  - ➢ *The consensus of experts in a 2010 review was that effective treatment of IS is defined by complete cessation of spasms and resolution of hypsarrhythmia on electroencephalography (EEG).*[E,7]
  - ➢ *A standard EEG to evaluate interictal activity may miss the hypsarrhythmia pattern, which can be variably present in an awake child, but is detected more sensitively in sleep. As a result, video-EEG monitoring is ideally used to assess treatment response in children with IS.*[7]

- ❒ Additional documentation as determined necessary by the Medical Director may be required

**4. Exclusion and Discontinuation of Treatment [ANY]**

Exclusion to, and discontinuation of, treatment if ANY of the following conditions applies: [ANY]

- ❑ Intolerable adverse effects or unacceptable toxicity from the drug. Examples of unaccaptable toxicity include the following: GI bleeding; gastric ulcer; hypertension; hypokalemia; severe depression; frank psychotic manifestations; posterior subcapsular cataracts; glaucoma
- ❑ Persistent and uncorrectable problems with adherence to treatment
- ❑ Poor response to treatment as evidenced by physical findings and/or clinical symptoms
- ❑ Contraindications/Exclusions to therapy
  - ❍ Non-FDA approved indications
  - ❍ Hypersensitivity to vigabatrin
  - ❍ Members with, or at high risk of, other types of irreversible vision loss or with other drugs associated with serious adverse ophthalmic effects, such as retinopathy or glaucoma unless the benefits clearly outweigh the risks

## ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

1. **Recommended Dosage [ONE]**
   - ❒ **Infantile Spasms:** For use as monotherapy in the treatment of infantile spasms in pediatric patients for whom the potential benefits outweigh the potential risk of vision loss
     - ❍ Initially, 50 mg/kg/day PO given in 2 divided doses. Titrate in 25 to 50 mg/kg/day increments every 3 days as needed for clinical response.
       - ➢ *Refer to Vigabatrin Oral Solution (50 mg/mL) Infant Dosing Table in Appendix 1.*
     - ❍ Max: 150 mg/kg/day. Use the lowest dose and shortest duration necessary to achieve clinical goals. Refer to package insert for recommended initial and maximum doses of the 50 mg/mL oral solution based on patient weight.

- *A post hoc analysis of a Canadian Pediatric Epilepsy Network study suggests vigabatrin therapy for a total duration of 6 months is adequate for treatment of infantile spasms; however, clinicians should use their clinical judgment regarding appropriate length of therapy.*[d]
- *Vigabatrin should be discontinued if a significant clinical response is not achieved within 2 to 4 weeks of initiation or if clinical failure is obvious earlier. If drug discontinuation is necessary, withdraw vigabatrin gradually (e.g., reduce the total daily dose by 25—50 mg/kg every 3 to 4 days*).
- *Vision loss in infants and children may not be detected until it is severe. Vision should be assessed at baseline (no later than 4 weeks after vigabatrin initiation), at least every 3 months during therapy, and approximately 3 to 6 months after vigabatrin discontinuation.*[a]

   - ❒ **Refractory Complex Partial Seizures (CPS)**
     - ❍ Adults (patients 17 years of age and older): Initiate at 1000 mg/day (500 mg twice daily); increase total daily dose weekly in 500 mg/day increments, to the recommended dose of 3000 mg/day (1500 mg twice daily). No additional benefit shown with 6 g daily compared with 3 g daily; higher incidence of adverse effects associated with 6 g daily.[a-e]
     - ❍ Pediatric (patients 10 to 16 years of age): Initiate at 500 mg/day (250 mg twice daily); increase total daily dose weekly in 500 mg/day increments, to the recommended maintenance dose of 2000 mg/day (1000 mg twice daily); patients weighing more than 60 kg should be dosed according to adult recommendations

   **NOTE:** The lowest dose and shortest exposure should be used that is consistent with clinical objectives. The possibility that vision loss from vigabatrin may be more common, more severe or have more severe functional consequences in infants and children than in adults cannot be excluded.[a]

2. **Authorization Limit [ALL]**
   - ❒ Quantity limit: [ONE]
     - ❍ 500 mg tablets: 180 units per 30 days (6 units per day)
     - ❍ 500 mg Powder Packets: 100 packets per 30 days
   - ❒ Dispensing limit: 30 days
   - ❒ Duration of initial authorization: [AS APPLICABLE TO DIAGNOSIS]
     - ❍ Infantile spasms (tablet formulation): 1 month
     - ❍ Refractory CPS (oral solution): 3 months
   - ❒ Continuation of treatment: Clinical benefit must be documented and vision testing must be performed regularly for continuation of therapy after initial authorization.
   - ❒ Duration of continuation of treatment: May be authorized up to **three (3) months**

3. **Route of Administration [ALL]**
   - ❒ Sabril (vigabatrin) is considered a **self-administered** medication.
   - ❒ If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare. Self-administered medications may not be dispensed

for self-administration and billed through the medical benefit by a provider; they must be dispensed through a participating pharmacy.

## COVERAGE EXCLUSIONS

All other uses of Sabril (vigabatrin) that are not an FDA-approved indication or FDA-approved indications that are not included in the 'Coverage Criteria' section of this policy are considered experimental/investigational or not a covered benefit of this policy. This is subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

## SUMMARY

**West Syndrome/Infantile Spasms (IS)**
The term "infantile spasms" is frequently used synonymously with West syndrome. Infantile spasms, or West syndrome, - is a rare disorder that includes a type of epileptic seizure and an electroencephalogram (EEG) finding called - hypsarrhythmia. Onset usually occurs before age of one. While the seizures generally resolve by the age of 3, long-term - prognosis is poor, with a high incidence of developmental delay, structural neurological abnormalities and persistent - seizure activity.[7] IS is characterized by epileptic spasms with onset in infancy or early childhood that are usually - associated with the electroencephalographic (EEG) pattern of hypsarrhythmia, and also developmental regression. -

The spasms are sudden, brief contractions of one or more muscle groups, and may be followed by a longer (less than 10 - seconds) tonic phase. Most often the spasms, involving the muscles of the neck, trunk and extremities, occur in clusters. - The intensity or the frequency of the spasms may increase progressively to a peak, decline, or cease. The clusters tend to - occur soon after arousal from sleep. -
The goal of infantile spasms treatment is to stop the seizures, normalize the EEG, and optimize the neurodevelopmental - outcome. -

Adverse effects with ACTH are potentially life threatening problems that include depression of the immune system and - modified response to infection leading to overwhelming sepsis. Minor side effects include behavioral changes especially - irritability, changes in appetite, weight gain and alteration in sleep patterns. -

**Pharmacologic Agents/Conventional Therapy**
Sabril is an irreversible inhibitor of gamma aminobutyric acid transaminase (GABA-T).[a] It is proposed that increasing the concentration of GABA within the central nervous system reduces seizure frequency. Sabril is the first drug to receive FDA approval for the treatment of IS as monotherapy. Due to the risk of permanent vision loss, the FDA requires a Risk Evaluation and Mitigation Strategy (REMS) program for this product. This program, called the SHARE program, includes periodic vision testing and a restricted distribution program.a Other treatment options for IS include corticosteroids, such as adrenocorticotropic hormone (ACTH) and prednisone.6 H.P.

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 partial seizures was changed to greater than or equal to 10 years of age.

## CLINICAL STUDIES

**Infantile Spasms (i.e., West Syndrome)**
The effectiveness of Sabril 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.[4] 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 (18-36mg/kg/day) or high-dose (100-148mg/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 50mg/kg/day with titration allowed to 150mg/kg/day) or placebo.[3] 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).

- There have been two pivotal trials conducted in the US which supported the approval of vigabatrin.

  The first of these studies was a double-blind, placebo controlled study, during which patients received 3 g of vigabatrin in addition to other anti-seizure medications (two on average).[1]
  - Previous therapy with either phenytoin or carbamazepine was a requirement for enrollment. Patients began with a 12-week evaluation period, during which a baseline was established.
  - The titration phase of therapy was next, where patients were randomized to receive either vigabatrin (n = 92) or placebo (n = 90). Over this four week phase patients were titrated to a dose of 2.5 g/day given in two divided doses.
  - Over the first week of the final 12-week segment, the vigabatrin dose was increased to 3 g/day.
  - The primary efficacy parameter was the number of seizures experienced per month during the final 8 weeks of the study. The decrease in seizure frequency for those taking vigabatrin was three per 28 days versus 0.8 per 28 days for those given placebo ($p = 0.0002$). Overall, the median seizure reduction was 39.5 versus 7.5% for vigabatrin and placebo respectively ($p > 0.001$). The mean number of seizure-free days in the vigabatrin group was 2.2 versus 0.5 for the placebo group($p = 0.0024$). A 50% reduction in mean monthly seizure frequency was achieved in 40 persons receiving vigabatrin, with five vigabatrin patients remaining seizure free at the end of the study period.

  A second study[2] evaluated the dose-response of vigabatrin in patients with uncontrolled CPS taking one or two additional anti-seizure medications [This study utilized three separate segments, the first of which included 12 weeks of pretreatment evaluation. The second segment was a 6-week titration phase, and the third segment was a maintenance phase of 12 additional weeks. Doses of vigabatrin included 1, 3 or 6 g/day (in divided doses) given to persons between the ages of 18 and 60 years with CPS (with or without secondary generalization; n = 149).
  - Patients were required to have used phenytoin or carbamazepine therapy with no response in seizure frequency. The primary outcome for this trial was the number of seizures occurring in during the final 8 weeks of segment 1 compared to the seizure frequency in the final 28-day of the study. The group receiving 1 g of vigabatrin experienced a mean reduction in seizure frequency of 0.8 ($p = 0.2$ versus placebo). Those receiving 3 or 6 g of vigabatrin had a decrease of 4.3 and 4.5 seizures respectively ($p < 0.0001$ vs placebo for both).
  - Therapeutic success (defined as at least a 50% reduction in seizure frequency) was achieved in 51 persons taking 3 g and 54 taking 6 g of vigabatrin ($p < 0.0001$ vs placebo). In the group receiving 1 g/day, 24 persons were considered to have experienced therapeutic success versus seven in the placebo group ($p = 0.0248$).

**Complex Partial Seizures in Adults**
The FDA approval of Sabril for the treatment of refractory complex partial seizures (CPS) was based on two clinical studies in patients with CPS, with or without secondary generalization, who were on an adequate and stable dose of an anticonvulsant, and had a history of failure on an adequate regimen of carbamazepine or phenytoin. Efficacy was based on the reduction in mean monthly frequency of complex partial seizures plus partial seizures secondarily generalized at end of study compared to baseline.

- Randomized, double-blind, placebo-controlled, parallel-group clinical studies with a total of 357 adults (age 18 to 60 years) with CPS, with or without secondary generalization were enrolled (Studies 1 and 2).
- Subjects 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.
- Subjects 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 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 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 6g/day vigabatrin administered twice daily. During the first six weeks following randomization, the dose was titrated upward beginning with 1g/day and increasing by 0.5g/day on days 1 and 5 of each subsequent week in the 3g/day and 6g/day groups, until the assigned dose was reached. The 3g/day and 6g/day dose groups were statistically significantly superior to placebo, but the 6g/day dose was not superior to the threeg/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 1g/day and increased by 0.5g/day on a weekly basis to the maintenance dose of 3g/day. Vigabatrin 3g/day was statistically significantly superior to placebo in reducing seizure frequency.

**Complex Partial Seizures in Patients 10 to 16 Years of Age**
Sabril 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 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. 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 adults 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.

**EVIDENCE REVIEWS**[G]

Treatment of IS has been evaluated in a 2004 and a 2012 American Academy of Neurology (AAN) practice parameter [Go, et.al,; Mackay,et.al)[B,C] a 2013 Cochrane systemic review [Hancock, et.al], and a 2010 United States consensus report (Pellock, et.al.].[D]

- Conclusions were limited by the overall poor methodology of the available studies.
- Lack of adherence to standardized case definitions and outcome measures is one problem with many studies. Another is that inclusion of a control group is critical, as the natural history of the disease is that clinical spasms subside and electroencephalogram patterns evolve without therapy, yet many clinicians would be reluctant not to treat as there is some observational data that delayed therapy may worsen prognosis.
- As a result, many questions still remain regarding the mechanism, optimal drug, dose, duration of therapy, and the importance of prompt initiation of treatment after the appearance of spasms.

A most up to date literature search shows lack of guidelines but presence of task force recommendations (AMR Review 2015).[G]

- A Task Force of the Commission of Pediatrics (Wilmshurst et.al.) developed a consensus document addressing diagnostic markers, management interventions, and outcome measures for infants with seizures.[F] Levels of evidence to support recommendations and statements were assessed using the American Academy of Neurology Guidelines and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

- According to the Task Force, 'There is no high level evidence to support any particular current agents for use in infants with seizures. Adrenocorticotropic hormone (ACTH) is preferred for short-term control of epileptic spasms (level B recommendation), oral steroids are probably effective in short-term control of spasms (level C recommendation), and a shorter interval from the onset of spasms to treatment initiation may improve long-term neurodevelopmental outcome (level C recommendation).'[F]

**American Academy of Neurology (AAN) and Child Neurology Society**[B]

In 2012 the American Academy of Neurology (AAN) and the Child Neurology Society published an evidence-based guideline which listed ACTH as a first-line agent for the short-term medical treatment of infantile spasms.[C] There are insufficient data to determine the optimal ACTH dose and duration of therapy, although short duration was preferable (i.e., approximately 2 weeks followed by taper).[D]

The American Academy of Neurology and Child Neurology Society (Mackay et al, 2004)[B] reviewed 159 articles to determine the current practice parameter on the medical treatment of infantile spasms. Outcome measures included complete cessation of spasms, resolution of hypsarrhythmia, relapse rate, developmental outcome, and presence or absence of epilepsy or an epileptiform EEG. The practice parameter concluded that:

i. - ACTH is probably an effective agent in the short-term treatment of infantile spasms, but there is insufficient evidence to recommend the optimum dosage and duration of treatment;
ii. - vigabatrin is possibly effective for the short-term treatment of infantile spasm and is possibly also effective for children with tuberous sclerosis;
iii. - there is insufficient evidence to recommend oral corticosteroids;
iv. - there is insufficient evidence to recommend any other treatment of infantile spasms, and
v. - there is insufficient evidence to conclude that successful treatment of infantile spasms improves the long-term prognosis.

**COCHRANE REVIEW**

Vigabatrin versus carbamazepine monotherapy for epilepsy

A Cochrane review was conducted to address the efficacy of vigabatrin in comparison to carbamazepine due to safety concerns with vigabatrin (visual field defects).[5] There were five studies involving a total of 734 participants which met the selection criteria of the group. The ability to perform a meta-analysis was complicated by all studies not reporting a common primary outcome as those chosen for the review. The final conclusion of the authors was that a significant benefit of vigabatrin over carbamazepine was proven, in terms of time to treatment withdrawal and time to achieve six-month remission after dose stabilization from randomization. Interestingly, results demonstrated a disadvantage for vigabatrin on time to first seizure after randomization. The authors concluded that due to significant safety concerns and lack of demonstrated superiority vigabatrin used as monotherapy for epilepsy should be undertaken with caution and not considered as a first-line choice.

Summary: Compared with carbamazepine for partial epilepsy, vigabatrin appears less effective but better tolerated (level 2 [mid-level] evidence as per Dynamed[e])

- Based on Cochrane review with limited evidence (most data from 1 randomized trial with high dropout rate)
- Systematic review of 5 randomized trials comparing vigabatrin to carbamazepine as monotherapy in 734 patients with epilepsy
    - all patients newly diagnosed with epilepsy
    - 4 trials included only patients with partial epilepsy
    - 4 trials did not have adequate randomization sequence generation and allocation concealment
    - 1 large trial (described below) considered high quality but had high dropout rate, other trials not summarized for efficacy outcomes
    - adverse events evaluated from 3 trials with 599 patients
        - no significant difference in rate of any adverse events (risk ratio 0.97, 95% CI 0.9-1.05)
        - vigabatrin associated with increased risk for weight gain (based on analysis of 2 trials with 511 patients)
        - vigabatrin associated with decreased risk for skin rash and drowsiness (based on analysis of 2 trials with 545 patients)
        - no significant differences in headache, dizziness, fatigue, insomnia, depression, leucopenia, visual field defects, visual disturbances, agitation, or amnesia
    - high rate of visual field defects reported with vigabatrin in systematic review of 32 observational studies
    - Reference: Cochrane Database Syst Rev 2012 Jan 18;(1):CD008781

Vigabatrin for refractory partial epilepsy[6]

An additional Cochrane review[6] included randomized, double-blind, placebo-controlled, fully published trials of vigabatrin in people with drug-resistant partial epilepsy. The analysis used intention-to-treat (ITT) with other outcomes including 50% or greater reduction in seizure frequency, treatment withdrawal and side effects observable in the short term. Eleven suitable trials that tested vigabatrin doses between 1000mg and 6000mg were identified and included in the analysis. There were 982 observations on 747 patients in the primary ITT analysis of treatment efficacy. Patients treated with vigabatrin were significantly more likely to obtain a 50% or greater reduction in seizure frequency compared with those treated with placebo (RR 2.58, 95% CI 1.87 to 3.57). Those treated with vigabatrin were also significantly more likely to have treatment withdrawn (RR 2.49, 95% CI 1.05 to 5.88), and were more likely to experience a number of side effects with fatigue and drowsiness being the most common. There was some evidence of small study effect bias, with smaller studies tending to report greater estimates of RR than larger studies. It is possible, therefore, that the actual RR of obtaining 50% reduction in seizure frequency is less than that obtained by a meta-analysis of fully published studies. Additionally, the trials evaluated were of relatively short duration so the long term efficacy and safety is not known from the trials used in this meta-analysis.

Summary: Vigabatrin appears to reduce seizure frequency in patients with drug-resistant partial epilepsy (level 2 [mid-level] evidence as per Dynamed[e])

- based on Cochrane review of trials with unclear allocation concealment

- systematic review of 11 randomized trials comparing vigabatrin 1,000-6,000 mg vs. placebo in 747 patients (982 observations) with drug-resistant partial epilepsy
- no trial gave clear details on methods for allocation concealment
- vigabatrin associated with
    - increased rate of ≥ 50% reduction in seizure frequency in analysis of 11 trials with 982 patients
        - risk ratio 2.58 (95% CI 1.87-3.57)
        - NNT 3-8 assuming ≥ 50% reduction in seizure frequency in 15% of controls
    - increased treatment withdrawals in analysis of 4 trials with 398 patients
    - increased fatigue and drowsiness in analysis of 11 trials with 995 patients
- no significant difference between groups in other side effects
- Reference - Cochrane Database Syst Rev 2013 Jan 31;(1):CD007302

**Hayes**
At the time of this writing, a Hayes assessment addressing Sabril and corresponding indications was not located or unavailable.

## DEFINITIONS

N/A -

## APPENDIX

**APPENDIX 1: Vigabatrin Oral Solution (50 mg/mL) Infant Dosing Table**
**Vigabatrin Oral Solution (50 mg/mL) Infant Dosing Table[d]**

| Weight (kg) | Starting Dosage (50 mg/kg daily) | Maximum Dosage (150 mg/kg daily) |
|---|---|---|
| 3 | 1.5 mL twice daily | 4.5 mL twice daily |
| 4 | 2 mL twice daily | 6 mL twice daily |
| 5 | 2.5 mL twice daily | 7.5 mL twice daily |
| 6 | 3 mL twice daily | 9 mL twice daily |
| 7 | 3.5 mL twice daily | 10.5 mL twice daily |
| 8 | 4 mL twice daily | 12 mL twice daily |
| 9 | 4.5 mL twice daily | 13.5 mL twice daily |
| 10 | 5 mL twice daily | 15 mL twice daily |
| 11 | 5.5 mL twice daily | 16.5 mL twice daily |
| 12 | 6 mL twice daily | 18 mL twice daily |
| 13 | 6.5 mL twice daily | 19.5 mL twice daily |
| 14 | 7 mL twice daily | 21 mL twice daily |
| 15 | 7.5 mL twice daily | 22.5 mL twice daily |
| 16 | 8 mL twice daily | 24 mL twice daily |

Reduce dosage gradually if discontinuing therapy.[a] In a controlled study in patients with infantile spasms, vigabatrin was tapered at a rate of 25–50 mg/kg daily every 3–4 days.[a]

Considerations in Subpopulations:
- Pediatrics: Safety and efficacy for treatment of complex partial seizures in pediatric patients <16 years of age not established
- Geriatrics: American Geriatrics Society (AGS) Beers Criteria recommends avoiding anticonvulsants (except for seizure disorders) in patients with history of falls or fractures due to risk of ataxia, impaired psychomotor function, syncope, and additional falls (AGS Strong recommendation, High quality evidence) (2012 AGS Beers Criteria for potentially inappropriate medication use in older adults [J Am Geriatr Soc 2012 Apr;60(4):616 full-text])

## Appendix 2: Antiepileptic Medications

| | |
|---|---|
| Carbamazepine | Lamotrigine |
| Divalproex | Levetiracetam |
| Ethosuximide | Oxcarbazepine |
| Felbamate (Felbatol) | Phenytoin |
| Valproic acid | Zonisamide |
| Topiramate | Gabapentin |
| Pregabalin (Lyrica) | |

**CODING INFORMATION:** THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

| HCPCS | Description |
|---|---|
| J3490 | Vigabatrin (Sabril) |

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