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Vigabatrin for Oral Solution

AA–Rated Generic Version of Sabril®

How was generic vigabatrin approved?

The following information was utilized by FDA in approving generic vigabatrin. Based on 21 CFR (the regulations; 21 CFR 320.22 and 21 CFR 320.24(b)(6)), standard bioequivalence studies were not needed to secure approval of generic vigabatrin. Instead, other mechanisms were used to establish that bioequivalence standards were met. These were as follows:

Any person submitting an abbreviated new drug application (ANDA) may request the US Food and Drug Administration (FDA) to waive the requirement for the submission of evidence measuring the *in vivo* bioavailability (BA) or demonstrating the *in vivo* bioequivalence (BE) of the drug product that is the subject of the application. A biowaiver means that *in vivo* BA/BE studies may be waived (not considered necessary for product approval). Instead of conducting expensive and time-consuming *in vivo* clinical studies, a dissolution test could be adopted as the surrogate basis for the decision as to whether the two pharmaceutical products are equivalent.

For certain drug products, the *in vivo* BA/BE of the drug product may be self-evident. FDA can waive the requirement for the submission of clinical study evidence obtained through measuring the *in vivo* BA/BE of these drug products. Vigabatrin's Powder for Oral Solution's *in vivo* BA/BE was considered self-evident by FDA based on the following data in the application:

1. **Vigabatrin Powder for Oral Solution, in packets of 500 mg, is intended to be reconstituted into solution and administered in the form of an oral solution.**
2. **Both the generic product and Sabril® contain the same active drug ingredient vigabatrin, in the same concentration of 500 mg powder (50 mg/mL when reconstituted), and in the same dosage form of powder for oral solution.**
3. **Both the generic product and Sabril® contain the same inactive ingredient povidone.**
4. **The active drug substance in vigabatrin has high permeability and is expected to have high solubility.**
5. **The generic product has rapid dissolution.**

Based on this evidence, FDA determined that Vigabatrin Powder for Oral Solution, in packets of 500 mg, was BE to the reference listed drug, Sabril®.

INDICATIONS

Vigabatrin for oral solution is indicated as adjunctive therapy for adults and pediatric patients 10 years of age and older with refractory complex partial seizures who have inadequately responded to several alternative treatments and for whom the potential benefits outweigh the risk of vision loss. Vigabatrin for oral solution is not indicated as a first line agent for complex partial seizures.

Vigabatrin for oral solution is indicated as monotherapy for pediatric patients with infantile spasms 1 month to 2 years of age for whom the potential benefits outweigh the potential risk of vision loss.

IMPORTANT SAFETY INFORMATION about vigabatrin for oral solution

WARNING: PERMANENT VISION LOSS

- **Vigabatrin can cause permanent bilateral concentric visual field constriction, including tunnel vision that can result in disability. In some cases, vigabatrin also can damage the central retina and may decrease visual acuity.**
- **The onset of vision loss from vigabatrin is unpredictable, and can occur within weeks of starting treatment or sooner, or at any time after starting treatment, even after months or years.**
- **Symptoms of vision loss from vigabatrin are unlikely to be recognized by patients or caregivers before vision loss is severe. Vision loss of milder severity, while often unrecognized by the patient or caregiver, can still adversely affect function.**
- **The risk of vision loss increases with increasing dose and cumulative exposure, but there is no dose or exposure known to be free of risk of vision loss.**
- **Vision assessment is recommended at baseline (no later than 4 weeks after starting vigabatrin), at least every 3 months during therapy, and about 3 to 6 months after the discontinuation of therapy.**
- **Once detected, vision loss due to vigabatrin is not reversible. It is expected that, even with frequent monitoring, some patients will develop severe vision loss.**

Please see additional Important Safety Information on next page.
Please see accompanying full Prescribing Information, including Boxed Warning and Medication Guide.

IMPORTANT SAFETY INFORMATION about vigabatrin for oral solution (continued)

- **Consider drug discontinuation, balancing benefit and risk, if vision loss is documented.**
- **Risk of new or worsening vision loss continues as long as vigabatrin is used. It is possible that vision loss can worsen despite discontinuation of vigabatrin.**
- **Because of the risk of vision loss, vigabatrin should be withdrawn from patients with refractory complex partial seizures who fail to show substantial clinical benefit within 3 months of initiation and within 2-4 weeks of initiation for patients with infantile spasms, or sooner if treatment failure becomes obvious. Patient response to and continued need for vigabatrin should be periodically reassessed.**
- **Vigabatrin should not be used in patients with, or at high risk of, other types of irreversible vision loss unless the benefits of treatment clearly outweigh the risks.**
- **Vigabatrin should not be used with other drugs associated with serious adverse ophthalmic effects such as retinopathy or glaucoma unless the benefits clearly outweigh the risks.**
- **Use the lowest dosage and shortest exposure to vigabatrin consistent with clinical objectives.**

Because of the risk of permanent vision loss, vigabatrin is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Vigabatrin REMS Program. Further information is available at www.vigabatrinREMS.com or call 1-866-244-8175.

- Abnormal magnetic resonance imaging (MRI) signal changes have been observed in some infants treated for infantile spasms with vigabatrin. These changes generally resolved with discontinuation of treatment, and resolved in a few patients despite continued use.
- Antiepileptic drugs (AEDs), including vigabatrin, increase the risk of suicidal thoughts and behavior. Monitor patients for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.
- As with all AEDs, discontinue vigabatrin gradually to avoid withdrawal seizures. However, if withdrawal is needed because of a serious adverse event, rapid discontinuation can be considered. Patients and caregivers should be told not to suddenly discontinue vigabatrin therapy.
- Vigabatrin can cause anemia, peripheral neuropathy, weight gain, and edema. Vigabatrin can cause somnolence and fatigue. Advise patients not to drive or operate machinery until they know how vigabatrin will affect them.
- In clinical studies of 4,079 vigabatrin-treated patients, the most common (≥5%) adverse reactions associated with the use of vigabatrin in combination with other AEDs were headache, somnolence, fatigue, dizziness, convulsion, nasopharyngitis, weight gain, upper respiratory tract infection, visual field defect, depression, tremor, nystagmus, nausea, diarrhea, memory impairment, insomnia, irritability, abnormal coordination, blurred vision, diplopia, vomiting, influenza, pyrexia, and rash.
- The adverse reactions most commonly associated with vigabatrin treatment discontinuation in ≥1% of patients were convulsion and depression.
- In patients with infantile spasms, the adverse reactions most commonly associated with vigabatrin treatment discontinuation in ≥1% of patients were infections, status epilepticus, developmental coordination disorder, dystonia, hypotonia, hypertonia, weight gain, and insomnia.
- Dose adjustment of phenytoin should be considered if clinically indicated, since vigabatrin may cause a moderate reduction in total phenytoin plasma levels. Vigabatrin may moderately increase the C_{max} of clonazepam resulting in an increase of clonazepam-associated adverse reactions.
- Suppression of alanine transaminase (ALT) and aspartate transaminase (AST) activity by vigabatrin may preclude the use of these markers, especially ALT, to detect early hepatic injury. Vigabatrin may increase the amount of amino acids in the urine, possibly leading to a false positive test for certain rare genetic metabolic diseases (e.g., alpha aminoadipic aciduria).
- Do not use vigabatrin during pregnancy unless the potential benefit justifies the potential risk to the fetus. **Pregnancy Registry:** To provide information regarding the effects of *in utero* exposure to vigabatrin, physicians should recommend that pregnant patients taking vigabatrin enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. Patients must call the toll-free number 1-888-233-2334 to enroll. Registry information can be found at **http://www.aedpregnancyregistry.org/**.
- Vigabatrin is excreted in human milk and may cause serious adverse events in nursing infants. Discontinue nursing or discontinue vigabatrin, taking into account the importance of the drug to the mother.
- Dose adjustment, including initiating treatment with a lower dose, is necessary in pediatric patients 10 years of age and older and adults with mild (creatinine clearance >50 to 80 mL/min), moderate (creatinine clearance >30 to 50 mL/min) and severe (creatinine clearance >10 to 30 mL/min) renal impairment.

Please see accompanying full Prescribing Information, including Boxed Warning and Medication Guide.

For more information, please call **833-PAR-HELP (833-727-4357)**.

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