PDL DRUG REVIEW

Proprietary Name: Sabril®
Common Name: vigabatrin
PDL Category: Anticonvulsants

Comparable Products	Preferred Drug List Status
Acthar	Non-Preferred with Conditions
Depakote ER	Preferred

Summary

Indications and Usage: As adjunctive therapy for adults and pediatric patients 10 years of age and older with refractory complex partial seizures (RCPS) who have inadequately responded to several alternative treatments and for whom the potential benefits outweigh the risk of vision loss; it is NOT indicated as a first line agent for complex partial seizures; AND 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.

This is a pregnancy category C medication.

Dosage Forms: Film-Coated Tablets: 500mg, AND Powder for Oral Solution: 500mg packets of granular powder

Recommended Dosage: Dosing is dependent on the indication, age group, weight, and dosage form. The tablet and powder for oral solution are bioequivalent. While either dosage form can be used for CPS, only the powder for oral solution should be used for infantile spasms. Tablets should not be used for this indication. *For RCPS in Adults >16 years*: Start at 500mg BID and titrate to a recommended dose of 1500mg BID. *For RCPS in Pediatric Patients 10-16 years*: Start at 250mg BID and titrate to a recommended dose of 1000mg BID. If pediatric patients weigh >60kg, then use the adult dosing recommendations. *Infantile Spasms*: Start at 50mg/kg/day given in 2 divided doses, titrated to a max dose of 150mg/kg/day given in 2 divided doses.

Dose adjustments are required for renal impairment, with specific requirements for mild (decrease dose by 25%), moderate (decrease dose by 50%), and severe renal impairment (decrease dose by 75%) in adults and pediatric patients ≥10 years of age. Information is not available for how to adjust doses in infants with renal impairment. The pharmacokinetics has not been studied in those with hepatic impairment.

Drug Interactions*:* Dose adjustments of phenytoin may be needed if used concomitantly with Sabril®, as Sabril® may cause a moderate reduction in total phenytoin plasma levels.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Sabril® 3000mg/day) minus reported % incidence for placebo in RCPS studies. Please note that an incidence of 0% means the incidence was the same or that the active drug was less than its comparator.* The most frequently reported adverse events included vertigo (1%), vision blurred (7%), diplopia (4%), asthenopia (2%), diarrhea (3%), nausea (2%), vomiting (1%), constipation (5%), abdominal pain (4%), fatigue (7%), asthenia (4%), peripheral edema

(4%), thirst (2%), nasopharyngitis (4%), urinary tract infection (4%), increased weight (3%), arthralgia (7%), back pain (2%), headache (2%), somnolence (9%), dizziness (7%), nystagmus (4%), tremor (7%), memory impairment (4%), abnormal coordination (5%), paraesthesia (6%), sedation (4%), depression (3%), confusional state (3%), depressed mood (4%), abnormal thinking (3%), dysmenorrhea (6%), pharyngolaryngeal pain (2%), and sinus headache (5%).

Contraindications: None listed

Manufacturer: Lundbeck

Analysis: Vigabatrin, the active ingredient of Sabril®, is an antiepileptic that does not have a precise mechanism of action. It is thought to work by acting as an irreversible inhibitor of γ-aminobutyric acid transaminase (GABA-T), the enzyme responsible for the metabolism of the inhibitory neurotransmitter GABA. This results in increased levels of GABA in the CNS.

Sabril® has a box warning regarding the increased risk of vision loss, as it may cause permanent bilateral concentric visual field constriction. Based on adult studies, ≥30% can be affected, ranging in severity from mild to severe. In some cases, it can also damage the central retina and may decrease visual acuity. The risk of vision loss increases with increasing dose and cumulative exposure. Vision should be assessed at baseline and every 3 months during therapy. Once vision loss is detected due to Sabril®, it is not reversible. It is recommended to discontinue treatment if visual loss is documented. It should not be used in patients with, or at high risk, of other types of irreversible vision loss unless the benefits clearly outweigh the risks. In addition, Sabril should not be used with other drugs associated with serious adverse ophthalmic effects such as retinopathy or glaucoma unless the benefits outweigh the risks. The box warning recommends that the lowest dose and shortest exposure to Sabril® consistent with clinical objectives be used.

Due to the increased risk of vision loss, Sabril® is only available through a special restricted distribution program called SHARE. This is also part of the box warning. The prescriber, providers, and patients must all be enrolled in the program by contacting the SHARE program at 1-888-45-SHARE. Upon enrollment, medication guides will be provided, and potential adverse events with Sabril® use must be reviewed. Vision must be assessed prior to starting therapy and then every 3 months thereafter during therapy, with subsequent discontinuation from therapy if there is no meaningful reduction in seizures or if patients do not comply with program requirements.

All anticonvulsants, including vigabatrin, may potentially increase the risk of suicidal thoughts and behaviors. Therefore, patients should be monitored for worsening of depression, changes in mood/behavior, and/or suicidal thoughts/behavior.

Two double-blind, placebo-controlled studies were performed to obtain FDA approval of Sabril® for treatment of RCPS in adults (N=357). Subjects had to be on a stable dose of an anticonvulsant, with a history of failure of an adequate regimen of either carbamazepine or phenytoin. The primary endpoint for the studies was the reduction in mean monthly frequency of CPS plus partial seizures secondarily generalized compared with baseline. With study 1, the 3g/day dose was statistically significantly superior to placebo for reduction in monthly frequency; however, the 6g/day dose was not superior to the 3gm/day dose. The table below, adapted from the prescribing information, illustrates the results for median monthly frequency of complex partial seizures.

	Sample Size	Baseline	Study end
Placebo	45	9	8.8
Sabril® 1g/day	45	8.5	7.7
Sabril® 3g/day	41	8.5	3.7*
Sabril® 6g/day	43	8.5	4.5*

*$p<0.05$ compared to placebo

In study 2, vigabatrin 3g/day was statistically significantly superior to placebo for reduction of monthly CPS.

	Sample Size	Baseline	Study end
Placebo	90	9.0	7.5
Sabril® 3g/day	92	8.3	5.5*

*p<0.05 compared to placebo

Three double-blind, placebo-controlled studies assessed the use of Sabril® for the treatment of CPS in pediatric patients aged 10-16 years. No individual study was considered adequately powered to determine efficacy in pediatric patients. The data from the 3 trials was pooled and used in a pharmacokinetic analysis, suggesting that a similar dose-response relationship exists between pediatric and adult patients when given as adjunctive therapy.

Two randomized studies were performed to obtain FDA approval of Sabril® for treatment of infantile spasms in the pediatric population. The first study was partially blinded (N=221). The primary endpoint was the number of patients who were spasm-free for 7 consecutive days beginning within the first 14 days of therapy. Results suggested that 17 patients in the high dose group (100-148mg/kg/day) experienced freedom from spasms compared with only 8 patients in the low dose group (18-36mg/kg/day), which was a statistically significant difference (p=0.0375). The second study (N=40) was a double-blind, placebo-controlled study, with the primary endpoint being the average percent change in daily spasm frequency, assessed during a consistent 2-hour window of evaluation comparing baseline to the final 2 days of the 5-day treatment phase. Statistically significant differences were not seen; however, a post-hoc analysis was done using a 24-hour clinical evaluation window. Results of this showed a statistically significant difference in the overall percentage of reductions in spasms between the vigabatrin (68.9%) and placebo (17.0%; p=0.030).

Place in Therapy: Sabril® is an anticonvulsant indicated for refractory complex partial seizures for use in those who have inadequately responded to several alternative treatments and for whom the potential benefits outweigh the risk of vision loss; it is NOT indicated as a first line agent for complex partial seizures. It is also indicated for infantile spasms.

It is recommended that Sabril remain non-preferred and require prior authorization to verify diagnosis and prior trial of preferred agents.

PDL Placement:

- ☐ **Preferred**
- ☒ **Non-Preferred**
- ☐ **Preferred with Conditions**

References

[1] Sabril [package insert]. Deerfield, IL: Lundbeck; 2013.