

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use SABRIL safely and effectively. See full prescribing information for SABRIL.

Sabril® (vigabatrin) for Oral Solution  
For Oral Administration Only  
Initial U.S. Approval: 2009



**WARNING: VISION LOSS**  
See full prescribing information for complete boxed warning

- SABRIL causes progressive and permanent bilateral concentric visual field constriction in a high percentage of patients. In some cases, SABRIL may also reduce visual acuity.
- Risk increases with total dose and duration of use, but no exposure to SABRIL is known that is free of risk of vision loss
- Risk of new and worsening vision loss continues as long as SABRIL is used, and possibly after discontinuing SABRIL
- Periodic vision testing is required for patients on SABRIL, but cannot reliably prevent vision damage
- Because of the risk of permanent vision loss, SABRIL is available only through a special restricted distribution program

**INDICATIONS AND USAGE**

SABRIL is an antiepileptic drug (AED) indicated for:

- Infantile Spasms (IS) - 1 Month to 2 Years of Age (1.1)

**DOSAGE AND ADMINISTRATION**

- Infantile Spasms: Initiate therapy at 50 mg/kg/day twice daily increasing total daily dose per instructions to a maximum of 150 mg/kg/day (2.1)
- Dose adjustment recommended in renally impaired patients (2.2)
- Reduce dose gradually upon discontinuation (2.3)

**DOSAGE FORM AND STRENGTHS**

Powder for Oral Solution: 500 mg (3.1)

**CONTRAINDICATIONS**

None (4)

**WARNINGS AND PRECAUTIONS**

- SABRIL causes permanent vision loss (5.1)
- Abnormal MRI signal changes have been reported in some infants with IS receiving SABRIL (5.3)
- Antiepileptic drugs, including SABRIL, increase the risk of suicidal thoughts and behavior (5.5)
- Dose should be tapered gradually to avoid withdrawal seizures (5.6)
- SABRIL causes anemia (5.7)
- SABRIL causes somnolence and fatigue (5.8)
- SABRIL causes peripheral neuropathy (5.9)
- SABRIL causes weight gain (5.10)
- SABRIL causes edema (5.11)

**ADVERSE REACTIONS**

Most common adverse reactions described in adults (change of ≥5% over placebo) in addition to permanent vision loss in adult controlled trials with vigabatrin were fatigue, somnolence, nystagmus, tremor, vision blurred, memory impairment, weight gain, arthralgia, abnormal coordination, and confusional state (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Lundbeck Inc. at 1-800-455-1141 or [www.lundbeckinc.com](http://www.lundbeckinc.com) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

**DRUG INTERACTIONS**

- Decreased phenytoin plasma levels have been reported (7.1)

**USE IN SPECIFIC POPULATIONS**

- Pregnancy: Based on animal data, may cause fetal harm. Pregnancy registry available (8.1)
- Nursing Mothers: SABRIL is excreted in human milk (8.2)
- Renal Impairment: Dose adjustment recommended (2.2, 8.4, 8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling (Medication Guide).

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### **WARNING: VISION LOSS**

- SABRIL causes permanent vision loss in infants, children and adults. Because assessing vision loss is difficult in children, the frequency and extent of vision loss in infants and children is poorly characterized. For this reason, the data described below is primarily based on the adult experience.
- In adults, SABRIL causes permanent bilateral concentric visual field constriction in 30 percent or more of patients that ranges in severity from mild to severe, including tunnel vision to within 10 degrees of visual fixation, and can result in disability. In some cases, SABRIL also can damage the central retina and may decrease visual acuity.
- 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.
- 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.
- It is possible that vision loss can worsen despite discontinuing SABRIL.
- Because of the risk of vision loss, SABRIL should be withdrawn 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. Patient response to and continued need for SABRIL should be periodically reassessed.
- In infants and children, vision loss may not be detected until it is severe. Nonetheless, 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. Once detected, vision loss due to SABRIL is not reversible. Vision testing is also required about 3 to 6 months after the discontinuation of SABRIL therapy.
- Symptoms of vision loss from SABRIL are unlikely to be recognized by the parent or caregiver before vision loss is severe. Vision loss of milder severity, although unrecognized by the caregiver, may still adversely affect function.
- SABRIL 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. The interaction of other types of irreversible vision damage with vision damage from SABRIL has not been well-characterized, but is likely adverse.
- SABRIL 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
- The lowest dose and shortest exposure to SABRIL should be used that is consistent with clinical objectives
- The possibility that vision loss from SABRIL may be more common, more severe or have more severe functional consequences in infants and children than in adults cannot be excluded.

Because of the risk of permanent vision loss, SABRIL is available only through a special restricted distribution program called SHARE, by calling 1-888-45-SHARE. Only prescribers and pharmacies registered with SHARE may prescribe and distribute SABRIL. In addition, SABRIL may be dispensed only to patients who are enrolled in and meet all conditions of SHARE [see WARNINGS AND PRECAUTIONS, Distribution Program for SABRIL (5.2)].

2  
3 **1 INDICATIONS AND USAGE**

4  
5 **1.1 Infantile Spasms (1 Month to 2 Years of Age)**

6 SABRIL<sup>®</sup> is indicated as monotherapy for pediatric patients with infantile spasms  
7 (IS) for whom the potential benefits outweigh the potential risk of vision loss [see  
8 WARNINGS AND PRECAUTIONS, Vision Loss (5.1)].

9  
10 **2 DOSAGE AND ADMINISTRATION**

11  
12 **2.1 Infantile Spasms (1 Month to 2 Years of Age)**

13 Physicians should review and discuss the Medication Guide with the caregiver(s)  
14 prior to preparation and administration of SABRIL. Physicians should confirm that  
15 caregiver(s) understand how to reconstitute SABRIL and to administer the correct  
16 dose to their infants.

17  
18 SABRIL should be given as twice daily oral administration with or without food.  
19 The initial dosing is 50 mg/kg/day given in two divided doses and can be titrated  
20 by 25-50 mg/kg/day increments every 3 days up to a maximum of 150 mg/kg/day  
21 [see USE IN SPECIFIC POPULATIONS, Pediatric Use (8.3)].

22  
23 The entire contents of the appropriate number of packets (500 mg/packet) of  
24 powder should be emptied into an empty cup, and should be dissolved in 10 mL  
25 of cold or room temperature water per packet using the 10 mL oral syringe  
26 supplied with the medication. The concentration of the final solution is 50  
27 mg/mL. Table 1 below describes how many packets and how many mL of water  
28 will be needed to prepare each individual dose. Each individual dose should be  
29 prepared immediately before use and administered cold or at room temperature.  
30

**Table 1. Number of Packages and mL of Water used for Each Individual Dose**

Each Individual Dose (Prepared and Given Twice Daily)	Number of Packets	Number of mL of Water for Dissolving
0 to 500 mg	1 packet	10 mL
501 to 1000 mg	2 packets	20 mL
1001 to 1500 mg	3 packets	30 mL

31  
32 Table 2 provides the volume that should be administered as individual doses in  
33 infants of various weights is presented below:  
34

**Table 2. Infant Dosing Table**

Weight (kg)	Starting Dose 50 mg/kg/day	Maximum Dose 150 mg/kg/day
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

**Table 2. Infant Dosing Table**

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

35

36

## **2.2 Patients with Renal Impairment**

37

38 SABRIL is primarily eliminated through the kidney. Information about how to  
39 adjust the dose in pediatric patients with renal impairment is unavailable.

40

41 The following dose adjustments are pertinent to the possible use of this dosage  
42 form in adults with renal impairment:

43

44 In patients with mild renal impairment (CL<sub>cr</sub> >50 to 80 mL/min), the dose should  
45 be decreased by 25%; in patients with moderate renal impairment (CL<sub>cr</sub> >30 to  
46 50 mL/min), the dose should be decreased by 50%; and in patients with severe  
47 renal impairment (CL<sub>cr</sub> >10 to <30 mL/min), the dose should be decreased by  
48 75%.

49

50 CL<sub>cr</sub> in mL/min may be estimated from a serum creatinine (mg/dL) determination  
51 using the following formula:

52

53  $CL_{cr} * = [140 - \text{age (years)}] \times \text{weight (kg)} / 72 \times \text{serum creatinine (mg/dL)}$

54

54  $*[\times 0.85 \text{ for female patients}]$

55

56 The effect of dialysis on SABRIL clearance has not been adequately studied.

57

58 [see CLINICAL PHARMACOLOGY, Pharmacokinetics, Renal Impairment (12.3)  
59 and USE IN SPECIFIC POPULATIONS, Renal Impairment (8.5)].

60

## **2.3 General Dosing Considerations**

62

63 Monitoring of SABRIL plasma concentrations to optimize therapy is not helpful. If  
64 a decision is made to discontinue SABRIL, the dose should be gradually  
65 reduced. In a controlled clinical study in patients with IS, vigabatrin was tapered  
66 by decreasing the dose at a rate of 25-50 mg/kg every 3-4 days [see  
67 WARNINGS AND PRECAUTIONS, Withdrawal of Antiepileptic Drugs (AEDs)  
68 (5.6)].

68

69

## **3 DOSAGE FORMS AND STRENGTHS**

70

71

### **3.1 Powder for Oral Solution**

72

500 mg Packet.

73

74 **4 CONTRAINDICATIONS**

75 None.

76

77 **5 WARNINGS AND PRECAUTIONS**

78

79 **5.1 Vision Loss (see BOXED WARNING)**

80 **Because of the risk of vision loss and because SABRIL, when it is effective,**  
81 **provides an observable symptomatic benefit, the patient who fails to show**  
82 **substantial clinical benefit within 2 to 4 weeks of initiation of treatment,**  
83 **should be withdrawn from SABRIL. If in the clinical judgment of the**  
84 **prescriber evidence of treatment failure becomes obvious earlier than 2 to**  
85 **4 weeks, treatment with SABRIL should be discontinued at that time.**  
86 **Patient response to and continued need for treatment should be**  
87 **periodically assessed.**

88 ***Monitoring of Vision***

89

90 Because vision testing in infants and children is difficult, vision loss may not be  
91 detected until it is severe. However, monitoring of vision by an ophthalmic  
92 professional with expertise in visual field interpretation and the ability to perform  
93 dilated indirect ophthalmoscopy of the retina, must be performed at baseline (no  
94 later than 4 weeks after starting SABRIL) and at least every 3 months while on  
95 therapy. Vision testing is also required about 3 to 6 months after the  
96 discontinuation of SABRIL therapy. This assessment should include visual acuity  
97 and visual field whenever possible.

98

99 The diagnostic approach should be individualized for the patient and clinical  
100 situation, but for all patients attempts to monitor vision periodically must be  
101 documented under the SHARE program. In patients in whom vision testing is not  
102 possible, treatment may continue according to clinical judgment, with appropriate  
103 caregiver(s) counseling, and with documentation in the SHARE program of the  
104 inability to test vision. Because of variability, results from ophthalmic monitoring  
105 must be interpreted with caution, and repeat testing is recommended if results  
106 are abnormal or uninterpretable.

107

108 The onset and progression of vision loss from SABRIL is unpredictable, and may  
109 occur or worsen precipitously. Once detected, vision loss due to SABRIL is not  
110 reversible.

111

112 **5.2 Distribution Program for SABRIL**

113 SABRIL is available only under a special restricted distribution program called  
114 the SHARE program. Under the SHARE program, only prescribers and  
115 pharmacies registered with the program are able to prescribe and distribute  
116 SABRIL. In addition, SABRIL may be dispensed only to patients who are enrolled  
117 in and meet all conditions of SHARE. Contact the SHARE program at 1-888-45-  
118 SHARE.

119

120 To enroll in SHARE, prescribers must understand the risks of SABRIL and  
121 complete the SHARE Prescriber Enrollment and Agreement Form indicating  
122 agreement to:

123

124 • Enroll all patients in SHARE

125 • Review the SABRIL Medication Guide with every caregiver

126 • Educate caregiver(s) on the risks of SABRIL, including the risk of vision loss  
127 [see BOXED WARNING: VISION LOSS]

128 • Arrange for visual field and retinal exam by an expert examiner and review  
129 visual evaluation prior to initiation of SABRIL treatment and every 3 months  
130 during therapy

131 • Remove patients from SABRIL therapy if the patients do not experience a  
132 meaningful reduction in seizures

133 • Counsel caregiver(s) who fail to comply with the program requirements

134 • Remove patients from SABRIL therapy whose caregiver(s) fail to comply with  
135 the program requirements after appropriate counseling

136

### 137 **5.3 Magnetic Resonance Imaging (MRI) Abnormalities**

138 Abnormal MRI signal changes characterized by increased T2 signal and  
139 restricted diffusion in a symmetric pattern involving the thalamus, basal ganglia,  
140 brain stem, and cerebellum have been observed in some infants treated for IS  
141 with SABRIL. In a retrospective epidemiologic study in infants with IS (N=205),  
142 the prevalence of these changes was 21.5% in SABRIL treated patients versus  
143 4.1% in patients treated with other therapies.

144

145 In the study above, in post marketing experience, and in published literature  
146 reports, these changes generally resolved with discontinuation of treatment. In a  
147 few patients, the lesion resolved despite continued use. It has been reported that  
148 some infants exhibited coincident motor abnormalities, but no causal relationship  
149 has been established and the potential for long-term clinical sequelae has not  
150 been adequately studied.

151

152 Neurotoxicity (including convulsions and hypomyelination) was observed in rats  
153 exposed to vigabatrin during late gestation and the neonatal and juvenile periods  
154 of development. The relationship between these findings and the abnormal MRI  
155 findings in infants treated for IS with vigabatrin is unknown [see WARNINGS  
156 AND PRECAUTIONS, Neurotoxicity (5.4) and USE IN SPECIFIC  
157 POPULATIONS, Pregnancy (8.1)].

158

159 The specific pattern of signal changes observed in IS patients was not observed  
160 in older children and adult patients treated with vigabatrin for refractory complex  
161 partial seizures (CPS). In a blinded review of MRI images obtained in prospective  
162 clinical trials in patients with refractory CPS 3 years and older (N=656), no  
163 difference was observed in anatomic distribution or prevalence of MRI signal  
164 changes between vigabatrin treated and placebo patients.

165

166 **5.4 Neurotoxicity**

167 Vacuolization, characterized by fluid accumulation and separation of the outer  
168 layers of myelin, has been observed in brain white matter tracts in adult and  
169 juvenile rats and adult mice, dogs, and possibly monkeys following administration  
170 of vigabatrin. This lesion, referred to as intramyelinic edema (IME), was seen in  
171 animals at doses within the human therapeutic range. A no-effect dose was not  
172 established in rodents or dogs. In the rat and dog, vacuolization was reversible  
173 following discontinuation of vigabatrin treatment, but, in the rat, pathologic  
174 changes consisting of swollen or degenerating axons, mineralization, and gliosis  
175 were seen in brain areas in which vacuolation had been previously observed.  
176 Vacuolization in adult animals was correlated with alterations in MRI and  
177 changes in visual and somatosensory evoked potentials (EP).

178

179 Administration of vigabatrin to rats during the neonatal and juvenile periods of  
180 development produced vacuolar changes in the gray matter (areas including the  
181 thalamus, midbrain, deep cerebellar nuclei, substantia nigra, hippocampus, and  
182 forebrain) which are considered distinct from the IME observed in vigabatrin  
183 treated adult animals. Decreased myelination, retinal dysplasia, and  
184 neurobehavioral abnormalities (convulsions, neuromotor impairment, learning  
185 deficits) were also observed following vigabatrin treatment of young rats. These  
186 effects occurred at doses associated with plasma vigabatrin levels substantially  
187 lower than those achieved clinically in infants and children.

188

189 In a published study, vigabatrin (200, 400 mg/kg/day) induced apoptotic  
190 neurodegeneration in the brain of young rats when administered by  
191 intraperitoneal injection on postnatal days 5-7.

192

193 Administration of vigabatrin to female rats during pregnancy and lactation at  
194 doses below those used clinically resulted in hippocampal vacuolation and  
195 convulsions in the mature offspring.

196

197 Abnormal MRI signal changes characterized by increased T2 signal and  
198 restricted diffusion in a symmetric pattern involving the thalamus, basal ganglia,  
199 brain stem, and cerebellum have been observed in some infants treated for IS  
200 with vigabatrin. Studies of the effects of vigabatrin on MRI and EP in adult  
201 epilepsy patients have demonstrated no clear-cut abnormalities [see WARNINGS  
202 AND PRECAUTIONS, MRI Abnormalities (5.3)].

203 **5.5 Suicidal Behavior and Ideation**

204 The following information is pertinent to the possible use of this dosage form in  
205 adults. Antiepileptic drugs (AEDs), including SABRIL, increase the risk of suicidal  
206 thoughts or behavior in patients taking these drugs for any indication. Patients  
207 treated with any AED for any indication should be monitored for the emergence  
208 or worsening of depression, suicidal thoughts or behavior, and/or any unusual  
209 changes in mood or behavior.

210

211 Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive  
212 therapy) of 11 different AEDs showed that patients randomized to one of the  
213 AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2,  
214 2.7) of suicidal thinking or behavior compared to patients randomized to placebo.  
215 In these trials, which had a median treatment duration of 12 weeks, the estimated  
216 incidence rate of suicidal behavior or ideation among 27,863 AED treated  
217 patients was 0.43%, compared to 0.24% among 16,029 placebo treated patients,  
218 representing an increase of approximately one case of suicidal thinking or  
219 behavior for every 530 patients treated. There were four suicides in drug treated  
220 patients in the trials and none in placebo treated patients, but the number is too  
221 small to allow any conclusion about drug effect on suicide.

222  
223 The increased risk of suicidal thoughts or behavior with AEDs was observed as  
224 early as one week after starting drug treatment with AEDs and persisted for the  
225 duration of treatment assessed. Because most trials included in the analysis did  
226 not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24  
227 weeks could not be assessed.

228  
229 The risk of suicidal thoughts or behavior was generally consistent among drugs  
230 in the data analyzed. The finding of increased risk with AEDs of varying  
231 mechanisms of action and across a range of indications suggests that the risk  
232 applies to all AEDs used for any indication. The risk did not vary substantially by  
233 age (5-100 years) in the clinical trials analyzed. Table 3 shows absolute and  
234 relative risk by indication for all evaluated AEDs.

235

**Table 3. Risk by Indication for Antiepileptic Drugs in the Pooled Analysis**

Indication	Placebo Patients with Events per 1000 Patients	Drug Patients with Events per 1000 Patients	Relative Risk: Incidence of Drug Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

236

237 The relative risk for suicidal thoughts or behavior was higher in clinical trials for  
238 epilepsy than in clinical trials for psychiatric or other conditions, but the absolute  
239 risk differences were similar for the epilepsy and psychiatric indications.

240

241 Anyone considering prescribing SABRIL or any other AED must balance the risk  
242 of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and  
243 many other illnesses for which AEDs are prescribed are themselves associated  
244 with morbidity and mortality and an increased risk of suicidal thoughts and  
245 behavior. Should suicidal thoughts and behavior emerge during treatment, the  
246 prescriber needs to consider whether the emergence of these symptoms in any  
247 given patient may be related to the illness being treated.

248

249 Patients, their caregiver(s), and families should be informed that AEDs increase  
250 the risk of suicidal thoughts and behavior and should be advised of the need to

251 be alert for the emergence or worsening of the signs and symptoms of  
252 depression, any unusual changes in mood or behavior, or the emergence of  
253 suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern  
254 should be reported immediately to healthcare providers.  
255

## 256 **5.6 Withdrawal of Antiepileptic Drugs (AEDs)**

257 As with all AEDs, SABRIL should be withdrawn gradually.

258

259 Caregivers should be told not to suddenly discontinue SABRIL therapy. In a  
260 controlled clinical study in patients with IS, vigabatrin was tapered by decreasing  
261 the daily dose at a rate of 25-50 mg/kg every 3-4 days [see DOSAGE AND  
262 ADMINISTRATION, General Dosing Considerations (2.3), PATIENT  
263 COUNSELING INFORMATION, Withdrawal of SABRIL Therapy (17.5)].  
264

## 265 **5.7 Anemia**

266 In North American controlled trials in adults, 5.7% of patients (16/280) receiving  
267 SABRIL and 1.6% of patients (3/188) receiving placebo had adverse events of  
268 anemia and/or met criteria for potentially clinically important hematology changes  
269 involving hemoglobin, hematocrit, and/or RBC indices. Across U.S. controlled  
270 trials, there were mean decreases in hemoglobin of about 3% and 0% in SABRIL  
271 and placebo-treated patients, respectively, and in hematocrit of about 1% in  
272 Sabril treated patients compared to a gain of about 1% in patients treated with  
273 placebo.  
274

275 In controlled and open label epilepsy trials in adults and pediatric patients, 3  
276 SABRIL patients (0.06%, 3/4855) discontinued for anemia and 2 SABRIL  
277 patients experienced unexplained declines in hemoglobin to below 8 g/dL and/or  
278 hematocrit below 24%.  
279

## 280 **5.8 Somnolence and Fatigue**

281 SABRIL causes somnolence and fatigue. Patients should be advised not to drive  
282 a car or operate other complex machinery until they are familiar with the effects  
283 of SABRIL on their ability to perform such activities.  
284

285 Pooled data from two SABRIL controlled trials in adults demonstrated that 24%  
286 (54/222) of SABRIL patients experienced somnolence compared to 10% (14/135)  
287 of placebo patients. In those same studies, 28% of SABRIL patients experienced  
288 fatigue compared to 15% (20/135) of placebo patients. Almost 1% of SABRIL  
289 patients discontinued from clinical trials for somnolence and almost 1%  
290 discontinued for fatigue.  
291

## 292 **5.9 Peripheral Neuropathy**

293 SABRIL has been shown to cause symptoms of peripheral neuropathy in adults.  
294 The clinical trials in pediatric patients were not adequately designed to assess  
295 whether or not these symptoms occur in the pediatric population.  
296

297 In a pool of North American controlled and uncontrolled epilepsy studies, 4.2%  
298 (19/457) of SABRIL treated patients developed signs and/or symptoms of  
299 peripheral neuropathy. In the subset of North American placebo controlled  
300 epilepsy trials, 1.4% (4/280) of SABRIL treated patients and no (0/188) placebo  
301 patients developed signs and/or symptoms of peripheral neuropathy. Initial  
302 manifestations of peripheral neuropathy in these trials included, in some  
303 combination, symptoms of numbness or tingling in the toes or feet, signs of  
304 reduced distal lower limb vibration or position sensation, or progressive loss of  
305 reflexes, starting at the ankles. Clinical studies in the development program were  
306 not designed to investigate peripheral neuropathy systematically and did not  
307 include nerve conduction studies, quantitative sensory testing, or skin or nerve  
308 biopsy. There is insufficient evidence to determine if development of these signs  
309 and symptoms were related to duration of SABRIL treatment, cumulative dose, or  
310 if the findings of peripheral neuropathy were completely reversible upon  
311 discontinuation of SABRIL.

312

### 313 **5.10 Weight Gain**

314 SABRIL has been shown to cause weight gain in adults. The clinical trials in  
315 pediatric patients were not adequately designed to assess whether or not weight  
316 gain occurs in the pediatric population.

317

318 Data pooled from randomized controlled trials found that 17% (77/443) of  
319 SABRIL patients gained  $\geq 7\%$  of baseline body weight versus 8% (22/275) of  
320 placebo patients. In these same trials, the mean weight change among SABRIL  
321 patients was 3.5 kg compared to 1.6 kg for placebo patients. In all epilepsy trials,  
322 0.6% (31/4855) of SABRIL patients discontinued for weight gain. The long term  
323 effects of SABRIL related weight gain are not known. Weight gain was not  
324 related to the occurrence of edema.

325

### 326 **5.11 Edema**

327 SABRIL has been shown to cause edema in adults. The clinical trials in pediatric  
328 patients were not adequately designed to assess whether or not edema occurs in  
329 the pediatric population.

330

331 Pooled data from controlled trials demonstrated increased risk among SABRIL  
332 patients compared to placebo patients for peripheral edema (SABRIL 2%,  
333 placebo 1%), and edema (SABRIL 1%, placebo 0%). In these studies, one  
334 SABRIL and no placebo patients discontinued for an edema related AE. There  
335 was no apparent association between edema and cardiovascular adverse events  
336 such as hypertension or congestive heart failure. Edema was not associated with  
337 laboratory changes suggestive of deterioration in renal or hepatic function.

338

## 339 **6 ADVERSE REACTIONS**

340 SABRIL causes permanent damage to vision in a high percentage of patients  
341 [see BOXED WARNING: VISION LOSS and WARNINGS AND PRECAUTIONS,  
342 Vision Loss (5.1)].

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**6.1 Adverse Reactions in Clinical Trials**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

**Adverse Events in U.S. and Primary Non-U.S. Clinical Studies**

In U.S. and primary non-U.S. clinical studies of 3139 adult and 999 pediatric patients treated with SABRIL, the most commonly observed ( $\geq 5\%$ ) adverse events associated with the use of SABRIL in combination with other AEDs were headache (18%), somnolence (17%), fatigue (16%), dizziness (15%), convulsion (11%), nasopharyngitis (10%), weight increased (10%), upper respiratory tract infection (10%), visual field defect (9%), depression (8%), tremor (7%), nystagmus (7%), nausea (7%), diarrhea (7%), memory impairment (7%), insomnia (7%), irritability (7%), coordination abnormal (7%), vision blurred (6%), diplopia (6%), vomiting (6%), influenza (6%), pyrexia (6%), and rash (6%).

The adverse reactions most commonly associated with SABRIL treatment discontinuation in  $\geq 1\%$  of IS patients were infections (1.5%), status epilepticus (1.2%), developmental coordination disorder (1.2%), dystonia (1.2%), hypotonia (1.2%), hypertonia (1.2%), weight increased (1.2%), and insomnia (1.2%).

**Most Common Adverse Reactions in Controlled Clinical Trials**

*Infantile Spasms*

In a randomized, placebo-controlled IS study with a 5 day double-blind treatment phase (n=40), the adverse events reported by >5% of SABRIL patients 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 otitis media acute (SABRIL 10%, placebo 0).

In 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. The treatment emergent adverse reactions ( $\geq 5\%$  in either dose group) are summarized in Table 4.

**Table 4. Treatment Emergent Adverse Events Occurring in  $\geq 5\%$  of Patients (Study 1A)**

Body System Event	SABRIL Low Dose [N = 114] %	SABRIL High Dose [N = 108] %
<b>Eye Disorders (other than field or acuity changes)</b>		
Strabismus	5	5
Conjunctivitis	5	2

**Table 4. Treatment Emergent Adverse Events Occurring in ≥5% of Patients (Study 1A)**

<b>Gastrointestinal Disorders</b>		
Vomiting	14	20
Constipation	14	12
Diarrhea	13	12
<b>General Disorders</b>		
Fever	29	19
<b>Infections</b>		
Upper respiratory tract infection	51	46
Otitis media	44	30
Viral infection	20	19
Pneumonia	13	11
Candidiasis	8	3
Ear infection	7	14
Gastroenteritis viral	6	5
Sinusitis	5	9
Urinary tract infection	5	6
Influenza	5	3
Croup infectious	5	1
<b>Metabolism &amp; Nutrition Disorders</b>		
Decreased appetite	9	7
<b>Nervous System Disorders</b>		
Sedation	19	17
Somnolence	17	19
Status epilepticus	6	4
Lethargy	5	7
Convulsion	4	7
Hypotonia	4	6
<b>Psychiatric Disorders</b>		
Irritability	16	23
Insomnia	10	12
<b>Respiratory Disorders</b>		
Nasal congestion	13	4
Cough	3	8
<b>Skin &amp; Subcutaneous Tissue Disorders</b>		
Rash	8	11

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*Refractory Complex Partial Seizures in Adults*

Because controlled trials in infants were of short duration and enrolled few patients, the adverse events from clinical trials in adults are presented. Table 5 lists the treatment emergent adverse reactions that occurred in ≥2% of SABRIL patients and that occurred more frequently than in placebo patients from 2 U.S. add-on clinical studies of refractory complex partial seizures in adults.

**Table 5. Treatment Emergent Adverse Reactions Occurring in ≥2% of SABRIL Patients and More Frequently than in Placebo Patients (Studies 024 and 025)**

Body System Preferred Term	SABRIL [N=222] %	Placebo [N=135] %
<b>Eye Disorders</b>		

**Table 5. Treatment Emergent Adverse Reactions Occurring in ≥2% of SABRIL Patients and More Frequently than in Placebo Patients (Studies 024 and 025)**

<b>Body System</b> Preferred Term	SABRIL [N=222] %	Placebo [N=135] %
Vision blurred	11	5
Diplopia	3	0
Eye disorder (other than field or acuity changes)	3	0
Asthenopia	2	0
<b>Gastrointestinal Disorders</b>		
Diarrhea	10	7
Nausea	9	8
Vomiting	7	6
Constipation	6	3
Abdominal pain upper	5	2
Dyspepsia	4	3
Stomach discomfort	3	1
Hemorrhoids	2	0
<b>General Disorders</b>		
Fatigue	27	16
Asthenia	5	2
Peripheral edema	5	1
Fever	5	3
<b>Infections</b>		
Nasopharyngitis	13	10
Upper respiratory tract infection	9	5
Influenza	5	4
Urinary tract infection	4	0
<b>Injury</b>		
Contusion	4	2
<b>Metabolism and Nutritional Disorders</b>		
Fluid retention	2	0
Increased appetite	2	0
Weight increased	8	3
<b>Musculoskeletal Disorders</b>		
Arthralgia	8	3
Back pain	6	2
Pain in extremity	5	4
Myalgia	3	2
Joint swelling	2	0
Muscle spasms	2	1
Shoulder pain	2	1
<b>Nervous System Disorders</b>		
Somnolence	22	13
Dizziness	21	17
Nystagmus	15	9
Tremor	14	8
Memory impairment	10	3
Coordination abnormal	9	2
Disturbance in attention	5	1
Sensory disturbance	5	2
Hyporeflexia	5	1
Parasthesia	5	1
Lethargy	4	2

**Table 5. Treatment Emergent Adverse Reactions Occurring in ≥2% of SABRIL Patients and More Frequently than in Placebo Patients (Studies 024 and 025)**

<b>Body System</b> Preferred Term	SABRIL [N=222] %	Placebo [N=135] %
Hypoaesthesia	3	2
Sedation	2	0
Status epilepticus	2	0
Dysarthria	2	1
<b>Psychiatric Disorders</b>		
Irritability	10	7
Depression	7	3
Confusional state	6	1
Depressed mood	4	1
Anxiety	4	3
Thinking abnormal	3	0
Abnormal behavior	3	1
Aggression	2	0
<b>Reproductive System</b>		
Dysmenorrhea	7	3
<b>Respiratory and Thoracic Disorders</b>		
Pharyngolaryngeal pain	9	5
Dyspnea	2	0
Sinus headache	4	1

388

389

## 6.2 Post Marketing Experience

390

The following serious adverse events have been reported since approval and use of SABRIL worldwide. All serious adverse events that are not listed above as adverse events reported in clinical trials, that are not relatively common in the population and are not too vague to be useful are listed in this section. These reactions are reported voluntarily from a population of uncertain size; therefore, it is not possible to estimate their frequency or establish a causal relationship to drug exposure. Events are categorized by system organ class.

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**Birth Defects:** Congenital cardiac defects, congenital external ear anomaly, congenital hemangioma, congenital hydronephrosis, congenital male genital malformation, congenital oral malformation, congenital vesicoureteric reflux, dentofacial anomaly, dysmorphism, fetal anticonvulsant syndrome, hamartomas, hip dysplasia, limb malformation, limb reduction defect, low set ears, renal aplasia, retinitis pigmentosa, supernumerary nipple, talipes

400

401

402

403

**Ear:** Deafness

404

405

**Endocrine:** Delayed puberty

406

407

**Gastrointestinal:** Gastrointestinal hemorrhage, esophagitis

408

409

**General:** Developmental delay, facial edema, malignant hyperthermia, multi-organ failure

410

411

412

413

414 **Hepatobiliary:** Cholestasis

415

416 **Nervous System:** Dystonia, encephalopathy, hypertonia, hypotonia, muscle  
417 spasticity, myoclonus, optic neuritis

418

419 **Psychiatric:** Acute psychosis, apathy, delirium, hypomania, neonatal agitation,  
420 psychotic disorder

421

422 **Respiratory:** Laryngeal edema, pulmonary embolism, respiratory failure, stridor

423

424 **Skin and Subcutaneous Tissue:** Angioedema, maculo-papular rash, pruritus

425

## 426 **7 DRUG INTERACTIONS**

427

428 For detailed information about Drug Interactions see CLINICAL  
429 PHARMACOLOGY, Pharmacokinetics, Drug Interactions (12.3).

430

### 431 **7.1 Phenytoin**

432 A 16% to 20% average reduction in total phenytoin plasma levels was reported in  
433 controlled clinical studies.

434

### 435 **7.2 Other AEDs**

436 There are no clinically significant pharmacokinetics interactions between SABRIL  
437 and either phenobarbital or sodium valproate. Based on population  
438 pharmacokinetics, carbamazepine, clonazepam, primidone, and sodium valproate  
439 appear to have no effect on plasma concentrations of vigabatrin.

440

### 441 **7.3 Clonazepam**

442 In a study of 12 healthy volunteers, clonazepam (0.5 mg) co-administration had  
443 no effect on SABRIL (1.5 g twice daily) concentrations. SABRIL increases the  
444 mean  $C_{max}$  of clonazepam by 30% and decreases the mean  $t_{max}$  by 45%.

445

### 446 **7.4 Oral Contraceptives**

447 SABRIL is unlikely to affect the efficacy of steroid oral contraceptives.

448

### 449 **7.5 Drug-Laboratory Test Interactions**

450 SABRIL decreases alanine transaminase (ALT) and aspartate transaminase  
451 (AST) plasma activity in up to 90% of patients. In some patients, these enzymes  
452 become undetectable. The suppression of ALT and AST activity by SABRIL may  
453 preclude the use of these markers, especially ALT, to detect early hepatic injury.

454

455 SABRIL may increase the amount of amino acids in the urine, possibly leading to  
456 a false positive test for certain rare genetic metabolic diseases (e.g., alpha  
457 aminoacidic aciduria).

458

459 **8 USE IN SPECIFIC POPULATIONS**

460

461 **8.1 Pregnancy**

462 The following information is pertinent to the possible use of this dosage form in  
463 adults.

464

465 Pregnancy Category C. Vigabatrin produced developmental toxicity, including  
466 teratogenic and neurohistopathological effects, when administered to pregnant  
467 animals at clinically relevant doses. In addition, developmental neurotoxicity was  
468 observed in rats treated with vigabatrin during a period of postnatal development  
469 corresponding to the third trimester of human pregnancy. There are no adequate  
470 and well-controlled studies in pregnant women. SABRIL should be used during  
471 pregnancy only if the potential benefit justifies the potential risk to the fetus.

472

473 Administration of vigabatrin (oral doses of 50 to 200 mg/kg) to pregnant rabbits  
474 throughout the period of organogenesis was associated with an increased  
475 incidence of malformations (cleft palate) and embryo-fetal death; these findings  
476 were observed in two separate studies. The no-effect dose for teratogenicity and  
477 embryoletality in rabbits (100 mg/kg) is approximately 1/2 the maximum  
478 recommended human dose (MRHD) of 3 g/day on a body surface area (mg/m<sup>2</sup>)  
479 basis for adults treated for refractory complex partial seizures with vigabatrin. In  
480 rats, oral administration of vigabatrin (50, 100, or 150 mg/kg) throughout  
481 organogenesis resulted in decreased fetal body weights and increased  
482 incidences of fetal anatomic variations. The no-effect dose for embryo-fetal  
483 toxicity in rats (50 mg/kg) is approximately 1/5 the MRHD in adults on a mg/m<sup>2</sup>  
484 basis. Oral administration of vigabatrin (50, 100, 150 mg/kg) to rats from the  
485 latter part of pregnancy through weaning produced long-term  
486 neurohistopathological (hippocampal vacuolation) and neurobehavioral  
487 (convulsions) abnormalities in the offspring. A no-effect dose for developmental  
488 neurotoxicity in rats was not established; the low-effect dose (50 mg/kg) is  
489 approximately 1/5 the MRHD in adults on a mg/m<sup>2</sup> basis.

490

491 In a published study, vigabatrin (300 or 450 mg/kg) was administered by  
492 intraperitoneal injection to a mutant mouse strain on a single day during  
493 organogenesis (day 7, 8, 9, 10, 11, or 12). An increase in malformations  
494 (including cleft palate) was observed at both doses.

495

496 Oral administration of vigabatrin (5, 15, or 50 mg/kg) to young rats during the  
497 neonatal and juvenile periods of development (postnatal days 4-65) produced  
498 neurobehavioral (convulsions, neuromotor impairment, learning deficits) and  
499 neurohistopathological (brain vacuolation, decreased myelination, and retinal  
500 dysplasia) abnormalities in treated animals. The early postnatal period in rats is  
501 generally thought to correspond to late pregnancy in humans in terms of brain  
502 development. The no-effect dose for developmental neurotoxicity in juvenile rats  
503 (5 mg/kg) was associated with plasma vigabatrin exposures (AUC) less than 1/30  
504 of those measured in pediatric patients receiving an oral dose of 50 mg/kg.

505

506 **Pregnancy Registry:** To provide information regarding the effects of *in utero*  
507 exposure to SABRIL, physicians are advised to recommend that pregnant patients  
508 taking SABRIL enroll in the North American Antiepileptic Drug (NAAED) Pregnancy  
509 Registry. This can be done by calling the toll free number 1-888-233-2334, and  
510 must be done by patients themselves. Information on the registry can also be  
511 found at the website <http://www.aedpregnancyregistry.org/>.

512

## 513 **8.2 Nursing Mothers**

514 The following information is pertinent to the possible use of this dosage form in  
515 adults.

516

517 Vigabatrin is excreted in human milk. Because of the potential for serious  
518 adverse reactions from vigabatrin in nursing infants [see WARNINGS AND  
519 PRECAUTIONS, MRI Abnormalities (5.3) and Neurotoxicity (5.4)], a decision  
520 should be made whether to discontinue nursing or to discontinue the drug, taking  
521 into account the importance of the drug to the mother.

522

## 523 **8.3 Pediatric Use**

524 SABRIL is indicated as monotherapy for pediatric patients with IS (1 month to 2  
525 years of age) for whom the potential benefits outweigh the potential risk for  
526 developing permanent vision loss.

527

528 Abnormal MRI signal changes characterized by increased T2 signal and  
529 restricted diffusion in a symmetric pattern involving the thalamus, basal ganglia,  
530 brain stem, and cerebellum have been observed in some infants treated for IS  
531 with vigabatrin. In a retrospective epidemiologic study in infants with IS (N=205),  
532 the prevalence of these changes was 21.5% in vigabatrin treated patients versus  
533 4.1% in patients treated with other therapies. A dose-dependent relationship may  
534 exist, as children with IS who were exposed to a higher vigabatrin dose ( $\geq 125$   
535 mg/kg/day) had a prevalence of 29.5%, while those exposed to lower doses of  
536 vigabatrin had a prevalence of 12.5%; however, these differences were not  
537 statistically significant ( $p=0.099$ ).

538

539 In the study above, in post marketing experience, and in published literature  
540 reports, these changes generally resolved with discontinuation of treatment,  
541 although in a few patients, the lesion resolved despite continued use. It has been  
542 reported that some infants exhibited coincident motor abnormalities, but no  
543 causal relationship has been established and the potential for long-term clinical  
544 sequelae has not been adequately studied [see WARNINGS AND  
545 PRECAUTIONS, MRI Abnormalities (5.3) and Neurotoxicity (5.4)].

546

547 The specific pattern of signal changes observed in IS patients was not observed  
548 in older children and adult patients treated with vigabatrin for refractory CPS. In a  
549 blinded review of MRI images obtained in prospective clinical trials in patients  
550 with refractory CPS 3 years and older (N=656), no difference was observed in

551 anatomic distribution or prevalence of MRI signal changes between vigabatrin  
552 treated and placebo patients.

553

554 Oral administration of vigabatrin (5, 15, or 50 mg/kg) to young rats during the  
555 neonatal and juvenile periods of development (postnatal days 4-65) produced  
556 neurobehavioral (convulsions, neuromotor impairment, learning deficits) and  
557 neurohistopathological (brain vacuolation, decreased myelination, and retinal  
558 dysplasia) abnormalities in treated animals. The no-effect dose for  
559 developmental neurotoxicity in juvenile rats (5 mg/kg) was associated with  
560 plasma vigabatrin exposures (AUC) less than 1/30 of those measured in pediatric  
561 patients receiving an oral dose of 50 mg/kg.

562

#### 563 **8.4 Geriatric Use**

564 The following information is pertinent to the possible use of this dosage form in  
565 adults.

566

567 Clinical studies of vigabatrin did not include sufficient numbers of patients aged  
568 65 and over to determine whether they responded differently from younger  
569 patients.

570

571 Vigabatrin is known to be substantially excreted by the kidney, and the risk of  
572 toxic reactions to this drug may be greater in patients with impaired renal  
573 function. Because elderly patients are more likely to have decreased renal  
574 function, care should be taken in dose selection, and it may be useful to monitor  
575 renal function.

576

577 Oral administration of a single dose of 1.5 g of vigabatrin to elderly (>65 years)  
578 patients with reduced creatinine clearance (<50 mL/min) was associated with  
579 moderate to severe sedation and confusion in 4 of 5 patients, lasting up to 5  
580 days. The renal clearance of vigabatrin was 36% lower in healthy elderly subjects  
581 (>65 years) than in young healthy males. Adjustment of dose or frequency of  
582 administration should be considered. Such patients may respond to a lower  
583 maintenance dose [see CLINICAL PHARMACOLOGY, Pharmacokinetics, Renal  
584 Impairment (12.3) and DOSAGE AND ADMINISTRATION, Patients with Renal  
585 Impairment (2.2)].

586

587 Other reported clinical experience has not identified differences in responses  
588 between the elderly and younger patients.

589

#### 590 **8.5 Renal Impairment**

591

592 Information about how to adjust the dose in pediatric patients with renal  
593 impairment is unavailable.

594

595 The following dose adjustments are pertinent to the possible use of this dosage  
596 form in adults with renal impairment:

597

598 In adults, dose adjustment, including initiating treatment with a lower dose, is  
599 necessary in patients with mild (creatinine clearance >50-80 mL/min), moderate  
600 (creatinine clearance >30-50 mL/min) and severe (creatinine clearance >10-30  
601 mL/min) renal impairment [see CLINICAL PHARMACOLOGY, Pharmacokinetics,  
602 Renal Impairment (12.3) and DOSAGE AND ADMINISTRATION, Patients with  
603 Renal Impairment (2.2)].

604

## 605 **9 DRUG ABUSE AND DEPENDENCE**

606

### 607 **9.1 Controlled Substance Class**

608 Vigabatrin is not a controlled substance.

609

### 610 **9.2 Abuse**

611 Vigabatrin did not produce adverse events or overt behaviors associated with  
612 abuse when administered to humans or animals. It is not possible to predict the  
613 extent to which a CNS active drug will be misused, diverted, and/or abused once  
614 marketed. Consequently, physicians should carefully evaluate patients for history  
615 of drug abuse and follow such patients closely, observing them for signs of  
616 misuse or abuse of vigabatrin (e.g., incrementation of dose, drug-seeking  
617 behavior).

618

### 619 **9.3 Dependence**

620 Following chronic administration of vigabatrin to animals, there were no apparent  
621 withdrawal signs upon drug discontinuation. However, as with all AEDs,  
622 vigabatrin should be withdrawn gradually to minimize increased seizure  
623 frequency [see WARNINGS AND PRECAUTIONS, Withdrawal of Antiepileptic  
624 Drugs (AEDs) (5.6) and PATIENT COUNSELING INFORMATION, Withdrawal of  
625 SABRIL Therapy (17.5)].

626

## 627 **10 OVERDOSAGE**

628

### 629 **10.1 Signs, Symptoms, and Laboratory Findings of Overdosage**

630 Confirmed and/or suspected vigabatrin overdoses have been reported during  
631 clinical studies and in post marketing surveillance. No vigabatrin overdoses  
632 resulted in death. When reported, the vigabatrin dose ingested ranged from 3 g  
633 to 90 g, but most were between 7.5 g and 30 g. Nearly half the cases involved  
634 multiple drug ingestions including carbamazepine, barbiturates,  
635 benzodiazepines, lamotrigine, valproic acid, acetaminophen, and/or  
636 chlorpheniramine.

637

638 Coma, unconsciousness, and/or drowsiness were described in the majority of  
639 cases of vigabatrin overdose. Other less commonly reported symptoms included  
640 vertigo, psychosis, apnea or respiratory depression, bradycardia, agitation,  
641 irritability, confusion, headache, hypotension, abnormal behavior, increased

642 seizure activity, status epilepticus, and speech disorder. These symptoms  
643 resolved with supportive care.

644

## 645 **10.2 Treatment or Management for Overdosage**

646 There is no specific antidote for SABRIL overdose. Standard measures to  
647 remove unabsorbed drug should be used, including elimination by emesis or  
648 gastric lavage. Supportive measures should be employed, including monitoring of  
649 vital signs and observation of the clinical status of the patients.

650

651 In an *in vitro* study, activated charcoal did not significantly adsorb vigabatrin.

652

653 The effectiveness of hemodialysis in the treatment of SABRIL overdose is  
654 unknown. In isolated case reports in renal failure patients receiving therapeutic  
655 doses of vigabatrin, hemodialysis reduced vigabatrin plasma concentrations by  
656 40% to 60%.

657

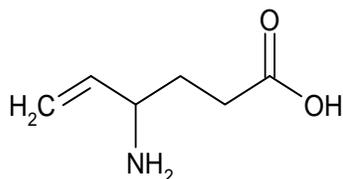
## 658 **11 DESCRIPTION**

659

**Table 6. Description**

---

Proprietary Name:	SABRIL <sup>®</sup>
Established Name:	Vigabatrin for Oral Solution
Dosage Form:	Packet
Route of Administration:	Oral
Pharmacologic Class of Drug:	Antiepileptic
Chemical Name:	(±) 4-amino-5-hexenoic acid
Structural Formula:	



---

660

661 SABRIL (vigabatrin) is available as a white granular powder for oral  
662 administration. Each packet contains 500 mg vigabatrin. Each packet also  
663 contains the inactive ingredient povidone. Vigabatrin is an oral antiepileptic drug  
664 with the chemical name (±) 4-amino-5-hexenoic acid. It is a racemate consisting  
665 of two enantiomers. The molecular formula is C<sub>6</sub>H<sub>11</sub>NO<sub>2</sub> and the molecular  
666 weight is 129.16.

667

668 Vigabatrin is a white to off-white powder which is freely soluble in water, slightly  
669 soluble in methyl alcohol, very slightly soluble in ethyl alcohol and chloroform,  
670 and insoluble in toluene and hexane. The pH of a 1% aqueous solution is about  
671 6.9. The n-octanol/water partition coefficient of vigabatrin is about 0.011  
672 ( $\log P = -1.96$ ) at physiologic pH. Vigabatrin melts with decomposition in a  
673 3-degree range within the temperature interval of 171°C to 176°C. The  
674 dissociation constants ( $pK_a$ ) of vigabatrin are 4 and 9.7 at room temperature  
675 (25°C).

## 676 **12 CLINICAL PHARMACOLOGY**

677

### 678 **12.1 Mechanism of Action**

679 The precise mechanism of vigabatrin's anti-seizure effect is unknown, but it is  
680 believed to be the result of its action as an irreversible inhibitor of  $\gamma$ -aminobutyric  
681 acid transaminase (GABA-T), the enzyme responsible for the metabolism of the  
682 inhibitory neurotransmitter GABA. This action results in increased levels of  
683 GABA in the central nervous system.

684

685 No direct correlation between plasma concentration and efficacy has been  
686 established. The duration of drug effect is presumed to be dependent on the rate  
687 of enzyme re-synthesis rather than on the rate of elimination of the drug from the  
688 systemic circulation.

689

### 690 **12.2 Pharmacodynamics**

691

#### 692 ***Effects on Electrocardiogram***

693 There is no indication of a QT/QTc prolonging effect of SABRIL in single doses  
694 up to 6.0 g. In a randomized, placebo-controlled, crossover study, 58 healthy  
695 adult subjects were administered a single oral dose of SABRIL (3 g and 6 g) and  
696 placebo. Peak concentrations for 6.0 g SABRIL were approximately 2-fold higher  
697 than the peak concentrations following the 3.0 g single oral dose.

698

### 699 **12.3 Pharmacokinetics**

700 Vigabatrin displayed linear pharmacokinetics after administration of single doses  
701 ranging from 0.5 g to 4 g, and after administration of repeated doses of 0.5 g to  
702 2.0 g twice daily. Bioequivalence has been established between the oral solution  
703 and tablet formulations.

704

#### 705 ***Absorption***

706 Following oral administration, vigabatrin is essentially completely absorbed.  
707 Time to maximum concentration ( $t_{max}$ ) is approximately 2.5 hours in infants and  
708 about 1 hour in children following a single dose. There was little accumulation  
709 with multiple dosing. A food effect study involving administration of vigabatrin to  
710 healthy adult volunteers under fasting and fed conditions indicated that the  $C_{max}$   
711 was decreased by 33%,  $t_{max}$  increased to 2 hours, and AUC was unchanged

712 under fed conditions [see DOSAGE AND ADMINISTRATION, Infantile Spasms  
713 (2.1)].

714

715 ***Distribution***

716 Vigabatrin does not bind to plasma proteins. Vigabatrin is widely distributed  
717 throughout the body; mean steady-state volume of distribution is 1.1 L/Kg (CV =  
718 20%).

719

720 ***Metabolism and Elimination***

721 Vigabatrin is not significantly metabolized; it is eliminated primarily through renal  
722 excretion. The half-life of vigabatrin in adults is about 7.5 hours and about 5.7  
723 hours in infants. Following administration of [<sup>14</sup>C]-vigabatrin to healthy adult male  
724 volunteers, about 95% of total radioactivity was recovered in the urine over 72  
725 hours with the parent drug representing about 80% of this. Vigabatrin induces  
726 CYP2C9, but does not induce other hepatic cytochrome P450 enzyme systems.

727

728 ***Pharmacokinetics in Special Populations***

729

730 ***Geriatric***

731 The renal clearance of vigabatrin in healthy elderly patients (≥ 65 years of age)  
732 was 36% less than those in healthy younger patients. A population PK analysis  
733 of patient data also confirmed these differences in age.

734

735 ***Pediatric***

736 The clearance of infants and children were 2.4±0.8 and 5.7±2.5 L/h,  
737 respectively compared to 7 L/h in adults.

738

739 ***Gender***

740 No gender differences were observed for the pharmacokinetic parameters of  
741 vigabatrin in patients.

742

743 ***Race***

744 No specific study was conducted to investigate the effects of race on SABRIL  
745 pharmacokinetics. A cross study comparison in adults between 23 Caucasian  
746 and 7 Japanese patients who received 1, 2, and 4 g of vigabatrin indicated that  
747 the AUC, C<sub>max</sub>, and half-life were similar for the two populations. However, the  
748 mean renal clearance of Caucasians (5.2 L/hr) was about 25% higher than the  
749 Japanese (4.0 L/hr). Inter-subject variability in renal clearance was 20% in  
750 Caucasians and was 30% in Japanese.

751

752 ***Renal Impairment***

753

754 There is no information available about the pharmacokinetics of vigabatrin in  
755 pediatric patients with renal impairment.

756

757 In adult patients with mild renal impairment (CLcr from >50-80 mL/min), mean  
758 AUC increased by 30% and the terminal half-life increased by 55% (8.1 hr vs  
759 12.5 hr) in comparison to the normal subjects. Mean AUC increased by two-  
760 fold and the terminal half-life increased by two-fold in patients with moderate  
761 renal impairment (CLcr from >30-50 mL/min) in comparison to the normal  
762 subjects. Mean AUC increased by 4.5-fold and the terminal half-life increased  
763 by 3.5-fold in patients with severe renal impairment (CLcr from >10-30 mL/min)  
764 in comparison to the normal subjects.

765

766 While dose adjustments are warranted in renally impaired pediatric patients, no  
767 data is available to guide dose adjustments in this patient population. Dosage  
768 adjustment in adults with renal impairment is recommended [see USE IN  
769 SPECIFIC POPULATIONS, Renal Impairment (8.5) and DOSAGE AND  
770 ADMINISTRATION, Patients with Renal Impairment (2.2)].

771

#### 772 *Hepatic Impairment*

773 Vigabatrin is not significantly metabolized. The pharmacokinetics of vigabatrin  
774 in patients with impaired liver function have not been studied.

775

#### 776 **Drug Interactions**

777

##### 778 *Phenytoin*

779 A 16% to 20% average reduction in total phenytoin plasma levels was reported  
780 in controlled clinical studies. *In vitro* drug metabolism studies indicate that  
781 decreased phenytoin concentrations upon addition of vigabatrin therapy are  
782 likely due to induction of cytochrome P450 2C enzymes in some patients.  
783 Although phenytoin dose adjustments are not routinely required, dose  
784 adjustment of phenytoin should be considered if clinically indicated.

785

##### 786 *Other AEDs*

787 When co-administered with vigabatrin, phenobarbital concentration (from  
788 phenobarbital or primidone) was reduced by an average of 8% to 16%, and  
789 sodium valproate plasma concentrations were reduced by an average of 8%.  
790 These reductions did not appear to be clinically relevant. Based on population  
791 pharmacokinetics, carbamazepine, clonazepam, primidone, and sodium  
792 valproate appear to have no effect on plasma concentrations of  
793 vigabatrin.

794

##### 795 *Clonazepam*

796 In a study of 12 healthy volunteers, clonazepam (0.5 mg) co-administration had  
797 no effect on SABRIL (1.5 g twice daily) concentrations. SABRIL increases the  
798 mean C<sub>max</sub> of clonazepam by 30% and decreases the mean t<sub>max</sub> by 45%.

799

##### 800 *Alcohol*

801 Co-administration of ethanol (0.6 g/kg) with vigabatrin (1.5 g twice daily)  
802 indicated that neither drug influences the pharmacokinetics of the other.

803

804 **Oral Contraceptives**

805 In a double-blind, placebo-controlled study using a combination oral  
806 contraceptive containing 30 µg ethinyl estradiol and 150 µg levonorgestrel,  
807 vigabatrin (3 g/day) did not interfere significantly with the cytochrome P450  
808 isoenzyme (CYP3A)-mediated metabolism of the contraceptive tested. Based  
809 on this study, vigabatrin is unlikely to affect the efficacy of steroid oral  
810 contraceptives. Additionally, no significant difference in pharmacokinetic  
811 parameters (elimination half-life, AUC, C<sub>max</sub>, apparent oral clearance, time to  
812 peak, and apparent volume of distribution) of vigabatrin were found after  
813 treatment with ethinyl estradiol and levonorgestrel.

814

815 **13 NONCLINICAL TOXICOLOGY**

816

817 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

818 Vigabatrin showed no carcinogenic potential in mouse or rat when given in the  
819 diet at doses up to 150 mg/kg/day for 18 months (mouse) or at doses up to 150  
820 mg/kg/day for 2 years (rat). These doses are less than the maximum  
821 recommended human dose (MRHD) for IS (150 mg/kg/day) and for refractory  
822 complex partial seizures in adults (3 g/day) on a mg/m<sup>2</sup> basis.

823

824 Vigabatrin was negative in *in vitro* (Ames, CHO/HGPRT mammalian cell forward  
825 gene mutation, chromosomal aberration assay in rat lymphocytes) and in *in vivo*  
826 (mouse bone marrow micronucleus) assays.

827

828 No adverse effects on male or female fertility were observed in rats at oral doses  
829 up to 150 mg/kg/day (approximately 1/2 the MRHD of 3 g/day (on a mg/m<sup>2</sup> basis)  
830 for adults treated for refractory complex partial seizures with vigabatrin.

831

832 **14 CLINICAL STUDIES**

833

834 **14.1 Infantile Spasms**

835 The effectiveness of SABRIL as monotherapy was established for IS in two  
836 multicenter controlled studies. Both studies were similar in terms of disease  
837 characteristics and prior treatments of patients and all enrolled infants had a  
838 confirmed diagnosis of IS.

839

840 **Study 1**

841

842 Study 1 (N=221) was a multicenter, randomized, low-dose high-dose, parallel  
843 group, partially-blinded (caregivers knew the actual dose but not whether their  
844 child was classified as low or high dose; EEG reader was blinded but  
845 investigators were not blinded) study to evaluate the safety and efficacy of  
846 vigabatrin in patients <2 years of age with new-onset Infantile Spasms. Patients  
847 with both symptomatic and cryptogenic etiologies were studied. The study was  
848 comprised of two phases. The first phase was a 14 to 21 day partially-blind

849 phase in which patients were randomized to receive either low- dose (18-  
850 36 mg/kg/day) or high-dose (100-148 mg/kg/day) vigabatrin. Study drug was  
851 titrated over 7 days, followed by a constant dose for 7 days. If the patient became  
852 spasm-free on or before day 14, another 7 days of constant dose was  
853 administered. The primary efficacy endpoint of this study was the proportion of  
854 patients who were spasm-free for 7 consecutive days beginning within the first  
855 14 days of vigabatrin therapy. Patients considered spasm-free were defined as  
856 those patients who remained free of spasms (evaluated according to caregiver  
857 response to direct questioning regarding spasm frequency) and who had no  
858 indication of spasms or hypersarrhythmia during 8 hours of CCTV EEG recording  
859 (including at least one sleep-wake-sleep cycle) performed within 3 days of the  
860 seventh day of spasm freedom and interpreted by a blinded EEG reader.  
861 Seventeen patients in the high dose group achieved spasm freedom compared  
862 with 8 patients in the low dose group. This difference was statistically significant  
863 ( $p=0.0375$ ). Primary efficacy results are shown in Table 7.  
864

**Table 7. Spasm Freedom by Primary Criteria (Study 1A)**

	SABRIL Treatment Group	
	18-36 mg/kg/day [N=114] n (%)	100-148 mg/kg/day [N=107] n (%)
Patients who Achieved Spasm Freedom	8 (7.0)	17 (15.9)

$p=0.0375$

Note: Primary criteria were evaluated based on caregiver assessment plus CCTV EEG confirmation within 3 days of the seventh day of spasm freedom.

865

## 866 **Study 2**

867

868 Study 2 (N=40) was a multicenter, randomized, double-blind, placebo-controlled,  
869 parallel group study consisting of a pre-treatment (baseline) period of 2-3 days,  
870 followed by a 5-day double-blind treatment phase during which patients were  
871 treated with vigabatrin (initial dose of 50 mg/kg/day with titration allowed to 150  
872 mg/kg/day) or placebo. The primary efficacy endpoint in this study was the  
873 average percent change in daily spasm frequency, assessed during a pre-  
874 defined and consistent 2-hour window of evaluation, comparing baseline to the  
875 final 2 days of the 5-day double-blind treatment phase. No statistically significant  
876 differences were observed in the average frequency of spasms using the 2-hour  
877 evaluation window. However, a post-hoc alternative efficacy analysis, using a 24-  
878 hour clinical evaluation window found a statistically significant difference in the  
879 overall percentage of reductions in spasms between the vigabatrin group (68.9%)  
880 and the placebo group (17.0%) ( $p=0.030$ ).

881

## 882 **15 REFERENCES**

883 None

884

## 885 **16 HOW SUPPLIED/STORAGE AND HANDLING**

886

887 **16.1 SABRIL Packet**

888 Each SABRIL packet contains 500 mg vigabatrin as a white to off-white granular  
889 powder.

890  
891 NDC 67386-211-65: Packages of 50.

892  
893 Store at 20-25°C (68-77°F). See USP controlled room temperature.

894  
895 **17 PATIENT COUNSELING INFORMATION**

896 See FDA-Approved Patient Labeling (17.6)

897  
898 Caregivers must be informed of the availability of a Medication Guide. They  
899 must be instructed to read the Medication Guide prior to initiating treatment with  
900 SABRIL and with each prescription refill. Doctors must review the SABRIL  
901 Medication Guide with every caregiver prior to initiation of treatment. Caregivers  
902 should be instructed to administer SABRIL only as prescribed.

903  
904 Physicians should confirm that caregiver(s) understand how to reconstitute  
905 SABRIL for Oral Solution and to administer the correct dose to their infants.

906  
907 **17.1 Vision Loss**

908 Caregiver(s) should be informed of the risk of permanent vision loss, particularly  
909 loss of peripheral vision, from SABRIL, and the need for monitoring vision [see  
910 WARNINGS AND PRECAUTIONS, Vision Loss (5.1)].

911  
912 Although vision testing in infants is insensitive, vision must be assessed to the  
913 extent possible at baseline (no later than 4 weeks after starting SABRIL) and at  
914 least every 3 months during therapy. Caregiver(s) should understand that vision  
915 testing is insensitive in infants and may not detect vision loss before it is severe.  
916 Caregiver(s) should also understand that if vision loss is documented, such loss  
917 is irreversible [see WARNINGS AND PRECAUTIONS, Vision Loss (5.1)].

918  
919 Caregiver(s) should be informed that if changes in vision are suspected, they  
920 should notify their physician immediately.

921  
922 **17.2 MRI Abnormalities**

923 Caregiver should be informed of the possibility of developing abnormal MRI  
924 signal changes of unknown clinical significance.

925  
926 **17.3 Suicidal Thinking and Behavior**

927 The following information is pertinent to the possible use of this dosage form in  
928 adults.

929  
930 Patients, their caregiver(s), and families should be counseled that AEDs,  
931 including SABRIL, may increase the risk of suicidal thoughts and behavior and  
932 should be advised of the need to be alert for the emergence or worsening of

933 symptoms of depression, any unusual changes in mood or behavior, or the  
934 emergence of suicidal thoughts, behavior, or thoughts of self-harm. Behaviors of  
935 concern should be reported immediately to healthcare providers [see  
936 WARNINGS AND PRECAUTIONS, Suicidal Behavior and Ideation (5.5)].

937

#### 938 **17.4 Use in Pregnancy**

939 The following information is pertinent to the possible use of this dosage form in  
940 adults.

941

942 Patients should be instructed to notify their physician if they become pregnant or  
943 intend to become pregnant during therapy, and to notify their physician if they are  
944 breast feeding or intend to breast feed during therapy [see USE IN SPECIFIC  
945 POPULATIONS, Pregnancy (8.1), Nursing Mothers (8.2)].

946

947 Patients should be encouraged to enroll in the NAAED Pregnancy Registry if  
948 they become pregnant. This registry is collecting information about the safety of  
949 antiepileptic drugs during pregnancy. To enroll, patients can call the toll free  
950 number 1-888-233-2334 [see USE IN SPECIFIC POPULATIONS, Pregnancy  
951 (8.1)]. Information on the registry can also be found at the website  
952 <http://www.aedpregnancyregistry.org/>.

953

#### 954 **17.5 Withdrawal of SABRIL Therapy**

955 Caregiver(s) should be told not to suddenly discontinue SABRIL therapy in their  
956 infant. As with all AEDs, withdrawal should be gradual. In a controlled clinical  
957 study in patients with IS, vigabatrin was tapered by decreasing the daily dose at  
958 a rate of 25-50 mg/kg every 3-4 days.

959

#### 960 **17.6 FDA-Approved Medication Guide**

961

962

963 Manufactured by: Patheon  
964 Cincinnati, OH 45237, U.S.A.

965

966 For: Lundbeck Inc.  
967 Deerfield, IL 60015, U.S.A.

968

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973 Issued: August 2009

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## MEDICATION GUIDE

### Sabril® (SAY-bril) (vigabatrin) Tablet

### Sabril® (SAY-bril) (vigabatrin) for Oral Solution

Read the Medication Guide that comes with SABRIL before you or your baby starts taking SABRIL and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your or your baby's medical condition or treatment.

#### What is the most important information I should know about SABRIL?

##### SABRIL can cause serious side effects, including:

1. **Permanent vision damage**
2. **Magnetic resonance imaging (MRI) changes**
3. **Risk of suicidal thoughts or actions**

#### 1. Permanent vision damage:

SABRIL can damage the vision of anyone who takes it. The most noticeable loss is in your ability to see to the side when you look 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 particularly to their peripheral vision. With severe vision loss you may only be able to see things straight in front of you (sometimes called 'tunnel vision'). You may also have blurry vision.

- **Vision loss and use of SABRIL in adults:** Because of the risk of vision loss, SABRIL is used to treat complex partial seizures (CPS) only in people who do not respond well enough to several other medicines.

#### Tell your doctor right away if you:

- think you are not seeing as well as before you started taking 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

These changes can mean that you have damage to your vision. Your doctor will test your visual fields (including peripheral vision) and visual acuity (ability to read an eye chart) before you start SABRIL or within 4 weeks after starting SABRIL, and at least every 3 months after that until SABRIL is stopped. Even if your vision seems fine, it is important that you get these regular vision tests because damage can happen to your vision before you notice any changes. These vision tests cannot prevent the vision damage that can happen with SABRIL, but they do allow you to stop SABRIL if vision has gotten worse, which usually will lessen further damage. If you do not have these vision tests regularly, your doctor may stop prescribing SABRIL for you. You should also have a vision test after SABRIL is stopped.

If you drive and your vision is damaged by SABRIL, driving might be more dangerous, or you may not be able to drive safely at all. You should discuss this with your doctor.

- **Vision loss in babies:** Because of the risk of vision loss, SABRIL is used in babies (1 month to 2 years old) with infantile spasms (IS) only when you and your doctor decide that

the possible benefits of SABRIL are more important than the risks. Parents or caregivers are not likely to recognize the symptoms of vision loss in babies until it is severe. Doctors may not find vision loss in babies until it is severe. It is difficult to test vision in babies, but all babies should have a vision test before starting SABRIL or within 4 weeks after starting SABRIL, and every 3 months after that until SABRIL is stopped. You should have a vision test for your baby after SABRIL is stopped.

**Tell your doctor right away if you think that your baby is:**

- not seeing as well as before taking SABRIL
- acting differently than normal

Even if your baby's vision seems fine, it is important to get regular vision tests because damage can happen before your baby acts differently. Even these regular vision exams may not show the damage to your baby's vision before it is serious and permanent. If your baby does not have these vision tests regularly, your doctor may stop prescribing SABRIL for your baby. If your baby is not able to complete vision testing, your doctor may continue prescribing SABRIL for your baby. But, your doctor will not be able to watch for vision loss in your baby.

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 doctor 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 doctors and patients only under a special program called SHARE. As part of the SHARE program, among other things, your doctor will have to test your or your baby's vision frequently while you or your baby are being treated with SABRIL, and even after you or your baby stops treatment. You also have to agree to be in the SHARE program, and agree to have your or your baby's vision tested regularly. Your doctor will explain the details of the SHARE program to you.

**2. Magnetic resonance imaging (MRI) changes:**

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.

**3. Risk of suicidal thoughts or actions:**

Like other antiepileptic drugs, SABRIL may cause suicidal thoughts or actions in a very small number of people, about 1 in 500 people taking it. Call a doctor right away if you have any of these symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety

- feeling agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

#### **How can I watch for early symptoms of suicidal thoughts and actions?**

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your doctor as scheduled.
- Call your doctor between visits as needed, especially if you are worried about symptoms.

#### **Do not stop SABRIL without first talking to a healthcare provider.**

- Stopping SABRIL suddenly can cause serious problems. Stopping a seizure medicine suddenly can cause seizures that will not stop (status epilepticus) in people who are being treated for seizures.

SABRIL can be prescribed only to people who are enrolled in a program called SHARE. Before you or your baby can begin taking SABRIL, you must read and agree to all of the instructions in the SHARE program.

#### **What is SABRIL?**

**SABRIL Tablets** is a prescription medicine used along with other treatments to treat adults with CPS if:

- The CPS does not respond well enough to several other treatments, and
- You and your doctor decide the possible benefit of taking SABRIL is more important than the risk of vision loss.

SABRIL should not be the first medicine used to treat your CPS.

**SABRIL for Oral Solution** is a prescription medicine used to treat babies, one month to two years old who have IS, if you and your doctor decide the possible benefits of taking SABRIL are more important than the possible risk of vision loss.

If you are an adult with CPS, you must sign an agreement form before you can receive SABRIL.

If you are the parent or caregiver of a baby with IS, you must sign an agreement form before your baby can receive SABRIL.

#### **What should I tell my doctor before starting SABRIL?**

**If you are an adult with CPS, before taking SABRIL tell your doctor** if you have or had:

- depression, mood problems or suicidal thoughts or behavior
- an allergic reaction to SABRIL, such as hives, itching, or trouble breathing
- any vision problems
- any kidney problems
- low red blood cell counts (anemia)
- any nervous or mental illnesses, such as depression, thoughts of suicide, or attempts at suicide
- any other medical conditions
- are breastfeeding or planning to breastfeed. SABRIL can pass into breast milk and may harm your baby. Talk to your healthcare provider about the best way to feed your baby if you take SABRIL.
- 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.

**Pregnancy Registry:**

If you become pregnant while taking SABRIL, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to collect information about the safety of antiepileptic medicine during pregnancy.

Before giving SABRIL to your baby, tell the doctor about all of your baby's medical conditions, including if your baby has or ever had:

- an allergic reaction to SABRIL, such as hives, itching, or trouble breathing
- any vision problems
- any kidney problems

**Tell your doctor about all the medicines you or your baby take**, including prescription and non-prescription medicines, vitamins, and herbal supplements. SABRIL and other medicines may affect each other causing side effects.

**How should I take SABRIL?**

**If you are an adult with CPS:**

- Your doctor will explain the SHARE Program to you
- You will receive SABRIL from a specialty pharmacy
- Take SABRIL tablets exactly as prescribed by your doctor. SABRIL tablets are usually taken two times each day.
- You may take SABRIL tablets with or without food
- Before you start taking SABRIL, talk to your doctor about what you should do if you miss a dose of SABRIL

- **Do not stop taking SABRIL suddenly.** This can cause serious problems. Stopping SABRIL or any seizure medicine suddenly can cause seizures that will not stop (status epilepticus) in people who are being treated for seizures. You should follow your doctor's instructions on how to stop taking SABRIL.
- Tell your doctor right away about any increase in seizures while you are stopping SABRIL
- If SABRIL does not improve your seizures enough within 3 months, your doctor will stop prescribing SABRIL for you
- **Do not stop taking SABRIL without talking to your doctor.** If SABRIL improves your seizures, you and your doctor should talk about whether the benefit of taking SABRIL is more important than the risk of vision loss, and decide if you will continue to take SABRIL.

**If you are giving SABRIL to your baby for IS:**

- Your doctor will explain the SHARE program to you
- You will receive SABRIL for oral solution from a specialty pharmacy
- Mix SABRIL for oral solution and give it to your baby exactly as prescribed by your doctor. Do not stop giving SABRIL for oral solution to your baby unless your doctor tells you to.
- SABRIL for oral solution is usually given two times each day
- SABRIL for oral solution can be given to your baby at the same time as their food, but the powder should not be mixed with their food. SABRIL for oral solution powder should be mixed with water only.
- See the end of this Medication Guide for detailed instructions for how to mix SABRIL for oral solution and give the medicine to your baby
- Before your baby starts taking SABRIL, speak to your baby's doctor about what to do if your baby misses a dose, vomits, spits up, or only takes part of the dose of SABRIL
- **Stopping SABRIL suddenly can cause serious problems.** Stopping SABRIL or any seizure medicine suddenly can cause seizures that will not stop. You should follow your doctor's instructions on how to stop giving SABRIL to your baby. SABRIL does not work in all babies. If your baby's seizures do not improve enough within 2 to 4 weeks, the doctor will stop SABRIL.
- **Tell your doctor right away about any increase in your baby's seizures while stopping SABRIL**

**What should I avoid while taking SABRIL?**

SABRIL causes sleepiness and tiredness. Adults taking SABRIL should not drive, operate machinery, or perform any hazardous task, unless you and your doctor have decided that you can do these things safely.

**What are the possible side effects of SABRIL?**

**SABRIL can cause serious side effects. See "What is the most important information I should know about SABRIL?"**

These other serious side effects happen in **adults**. It is not known if these side effects also happen in babies who take SABRIL.

- Low red blood cell counts (anemia)

- Sleepiness and tiredness. See “What should I avoid while taking SABRIL?”
- Nerve problems. Symptoms of a nerve problem can include numbness and tingling in your toes or feet. It is not known if nerve problems will go away after you stop taking SABRIL.
- Weight gain that happens without swelling
- Swelling

**If you are an adult with CPS, SABRIL may make certain types of seizures worse. Tell your doctor right away if your seizures get worse.**

The most common side effects of SABRIL in adults include:

- problems walking or feel uncoordinated
- feel dizzy
- shaking (tremor)
- joint pain
- memory problems and not thinking clearly
- eye problems: blurry vision, double vision and eye movements that you cannot control

**If you are giving SABRIL to your baby for IS**

SABRIL may make certain types of seizures worse. You should tell your baby’s doctor right away if your baby’s seizures get worse. Tell your baby’s doctor if you see any changes in your baby’s behavior.

The most common side effects of SABRIL in **babies and young children** include:

- sleepiness - SABRIL may cause your baby to be sleepy. Sleepy babies may have a harder time suckling and feeding, or may be irritable.
- ear infection
- irritability

Tell your doctor if you or your baby have any side effect that bother you or that does not go away. These are not all the possible side effects of SABRIL. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store SABRIL?**

Store SABRIL tablets and SABRIL packets at room temperature, between 68°F to 77°F (20°C to 25°C).

Keep SABRIL tablets and SABRIL powder in the container they come in.

**Keep SABRIL and all medicines out of the reach of children.**

**General information about SABRIL**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use SABRIL for a condition for which it was not prescribed. Do not give SABRIL to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about SABRIL. If you would like more information about SABRIL, talk with your doctor. You can ask your pharmacist or doctor for information about SABRIL that is written for health professionals. For more information, go to **www.SABRIL.net** or call **1-800-455-1141**.

### **What are the ingredients in SABRIL?**

Active Ingredient: vigabatrin.

Inactive Ingredients in **SABRIL tablets**: hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycols, povidone, sodium starch glycolate, and titanium dioxide.

Inactive Ingredient in **SABRIL powder**: povidone.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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