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HIGHLIGHTS OF PRESCRIBING INFORMATION

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

POTIGA (ezogabine) Tablets, CV
Initial U.S. Approval: 2011

INDICATIONS AND USAGE

POTIGA is a potassium channel opener indicated as adjunctive treatment of partial-onset seizures in patients aged 18 years and older. (1)

DOSAGE AND ADMINISTRATION

- Administer in 3 divided doses daily, with or without food. (2)
- The initial dosage should be 100 mg 3 times daily (300 mg per day) for 1 week. (2)
- Titrate to maintenance dosage by increasing the dosage at weekly intervals by no more than 150 mg per day. (2)
- Optimize effective dosage between 200 mg 3 times daily (600 mg per day) to 400 mg 3 times daily (1,200 mg per day). (2)
- In controlled clinical trials, 400 mg 3 times daily (1,200 mg per day) showed limited improvement compared to 300 mg 3 times daily (900 mg per day) with an increase in adverse reactions and discontinuations. (2)
- When discontinuing POTIGA, reduce the dosage gradually over a period of at least 3 weeks. (2, 5.6)
- Dosing adjustments are required for geriatric patients and patients with moderate to severe renal or hepatic impairment. (2)

DOSAGE FORMS AND STRENGTHS

Tablets: 50 mg, 200 mg, 300 mg, and 400 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Urinary retention: Patients should be carefully monitored for urologic symptoms. (5.1)
- Neuropsychiatric symptoms: Monitor for confusional state, psychotic

symptoms, and hallucinations. (5.2)

- Dizziness and somnolence: Monitor for dizziness and somnolence. (5.3)
- QT prolongation: QT interval should be monitored in patients taking concomitant medications known to increase the QT interval or with certain heart conditions. (5.4)
- Suicidal behavior and ideation: Monitor for suicidal thoughts or behaviors. (5.5)

ADVERSE REACTIONS

The most common adverse reactions (incidence $\geq 4\%$ and approximately twice placebo) are dizziness, somnolence, fatigue, confusional state, vertigo, tremor, abnormal coordination, diplopia, disturbance in attention, memory impairment, asthenia, blurred vision, gait disturbance, aphasia, dysarthria, and balance disorder. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Ezogabine plasma levels may be reduced by concomitant administration of phenytoin or carbamazepine. An increase in dosage of POTIGA should be considered when adding phenytoin or carbamazepine. (7.1)
- N-acetyl metabolite of ezogabine may inhibit renal clearance of digoxin, a P-glycoprotein substrate. Monitor digoxin levels. (7.2)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. Pregnancy registry available. (8.1)
- Pediatric use: Safety and effectiveness in patients under 18 years of age have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE.

Revised:06/2013

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*Sections or subsections omitted from the full prescribing information are not listed.

1 **FULL PRESCRIBING INFORMATION**

2 **1 INDICATIONS AND USAGE**

3 POTIGA™ is indicated as adjunctive treatment of partial-onset seizures in patients aged
4 18 years and older.

5 **2 DOSAGE AND ADMINISTRATION**

6 The initial dosage should be 100 mg 3 times daily (300 mg per day). The dosage should
7 be increased gradually at weekly intervals by no more than 50 mg 3 times daily (increase in the
8 daily dose of no more than 150 mg per day) up to a maintenance dosage of 200 mg to 400 mg 3
9 times daily (600 mg to 1,200 mg per day), based on individual patient response and tolerability.
10 This information is summarized in Table 1 under General Dosing. In the controlled clinical trials,
11 400 mg 3 times daily showed limited evidence of additional improvement in seizure reduction,
12 but an increase in adverse events and discontinuations, compared to the 300 mg 3 times daily
13 dosage. The safety and efficacy of doses greater than 400 mg 3 times daily (1,200 mg per day)
14 have not been examined in controlled trials.

15 No adjustment in dosage is required for patients with mild renal or hepatic impairment
16 (see General Dosing, Table 1). Dosage adjustment is required in patients with moderate and
17 greater renal or hepatic impairment (see Dosing in Specific Populations, Table 1).

18 POTIGA should be given orally in 3 equally divided doses daily, with or without food.

19 POTIGA Tablets should be swallowed whole.

20 If POTIGA is discontinued, the dosage should be gradually reduced over a period of at
21 least 3 weeks, unless safety concerns require abrupt withdrawal.

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23 **Table 1. Dosing Recommendations**

Specific Population	Initial Dose	Titration	Maximum Dose
General Dosing			
<u>General population</u> (including patients with mild renal or hepatic impairment)	100 mg 3 times daily (300 mg per day)	Increase by no more than 50 mg 3 times daily, at weekly intervals	400 mg 3 times daily (1,200 mg per day)
Dosing in Specific Populations			
<u>Geriatrics</u> (patients >65 years)	50 mg 3 times daily (150 mg per day)	Increase by no more than 50 mg 3 times daily, at weekly intervals	250 mg 3 times daily (750 mg per day)
<u>Renal impairment</u> (patients with CrCL <50 mL per min or end-stage renal disease on dialysis)	50 mg 3 times daily (150 mg per day)		200 mg 3 times daily (600 mg per day)
<u>Hepatic impairment</u> (patients with Child-Pugh 7-9)	50 mg 3 times daily (150 mg per day)		250 mg 3 times daily (750 mg per day)
<u>Hepatic impairment</u> (patients with Child-Pugh >9)	50 mg 3 times daily (150 mg per day)		200 mg 3 times daily (600 mg per day)

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25 **3 DOSAGE FORMS AND STRENGTHS**

- 26 50 mg, purple, round, film-coated tablets debossed with “RTG 50” on one side.
 27 200 mg, yellow, oblong, film-coated tablets debossed with “RTG-200” on one side.
 28 300 mg, green, oblong, film-coated tablets debossed with “RTG-300” on one side.
 29 400 mg, purple, oblong, film-coated tablets debossed with “RTG-400” on one side.

30 **4 CONTRAINDICATIONS**

31 None.

32 **5 WARNINGS AND PRECAUTIONS**

33 **5.1 Urinary Retention**

34 POTIGA caused urinary retention in clinical trials. Urinary retention was generally
 35 reported within the first 6 months of treatment, but was also observed later. Urinary retention
 36 was reported as an adverse event in 29 of 1,365 (approximately 2%) patients treated with
 37 POTIGA in the open-label and placebo-controlled epilepsy database [*see Clinical Studies (14)*].
 38 Of these 29 patients, 5 (17%) required catheterization, with post-voiding residuals of up to
 39 1,500 mL. POTIGA was discontinued in 4 patients who required catheterization. Following

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40 discontinuation, these 4 patients were able to void spontaneously; however, 1 of the 4 patients
41 continued intermittent self-catheterization. A fifth patient continued treatment with POTIGA and
42 was able to void spontaneously after catheter removal. Hydronephrosis occurred in 2 patients,
43 one of whom had associated renal function impairment that resolved upon discontinuation of
44 POTIGA. Hydronephrosis was not reported in placebo patients.

45 In the placebo-controlled epilepsy trials, “urinary retention,” “urinary hesitation,” and
46 “dysuria” were reported in 0.9%, 2.2%, and 2.3% of patients on POTIGA, respectively, and in
47 0.5%, 0.9%, and 0.7% of patients on placebo, respectively.

48 Because of the increased risk of urinary retention on POTIGA, urologic symptoms should
49 be carefully monitored. Closer monitoring is recommended for patients who have other risk
50 factors for urinary retention (e.g., benign prostatic hyperplasia [BPH]), patients who are unable
51 to communicate clinical symptoms (e.g., cognitively impaired patients), or patients who use
52 concomitant medications that may affect voiding (e.g., anticholinergics). In these patients, a
53 comprehensive evaluation of urologic symptoms prior to and during treatment with POTIGA
54 may be appropriate.

55 **5.2 Neuro-Psychiatric Symptoms**

56 Confusional state, psychotic symptoms, and hallucinations were reported more frequently
57 as adverse reactions in patients treated with POTIGA than in those treated with placebo in
58 placebo-controlled epilepsy trials (see Table 2). Discontinuations resulting from these reactions
59 were more common in the drug-treated group (see Table 2). These effects were dose-related and
60 generally appeared within the first 8 weeks of treatment. Half of the patients in the controlled
61 trials who discontinued POTIGA due to hallucinations or psychosis required hospitalization.
62 Approximately two-thirds of patients with psychosis in controlled trials had no prior psychiatric
63 history. The psychiatric symptoms in the vast majority of patients in both controlled and open-
64 label trials resolved within 7 days of discontinuation of POTIGA. Rapid titration at greater than
65 the recommended doses appeared to increase the risk of psychosis and hallucinations.

66

67 **Table 2. Major Neuro-Psychiatric Symptoms in Placebo-Controlled Epilepsy Trials**

Adverse Reaction	Number (%) With Adverse Reaction		Number (%) Discontinuing	
	POTIGA (n = 813)	Placebo (n = 427)	POTIGA (n = 813)	Placebo (n = 427)
Confusional state	75 (9%)	11 (3%)	32 (4%)	4 (<1%)
Psychosis	9 (1%)	0	6 (<1%)	0
Hallucinations ^a	14 (2%)	2 (<1%)	6 (<1%)	0

68 ^a Hallucinations includes visual, auditory, and mixed hallucinations.

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70 **5.3 Dizziness and Somnolence**

71 POTIGA causes dose-related increases in dizziness and somnolence [*see Adverse*
72 *Reactions (6.1)*]. In placebo-controlled trials in patients with epilepsy, dizziness was reported in

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73 23% of patients treated with POTIGA and 9% of patients treated with placebo. Somnolence was
74 reported in 22% of patients treated with POTIGA and 12% of patients treated with placebo. In
75 these trials 6% of patients on POTIGA and 1.2% on placebo discontinued treatment because of
76 dizziness; 3% of patients on POTIGA and <1.0% on placebo discontinued because of
77 somnolence.

78 Most of these adverse reactions were mild to moderate in intensity and occurred during
79 the titration phase. For those patients continued on POTIGA, dizziness and somnolence appeared
80 to diminish with continued use.

81 **5.4 QT Interval Effect**

82 A study of cardiac conduction showed that POTIGA produced a mean 7.7-msec QT
83 prolongation in healthy volunteers titrated to 400 mg 3 times daily. The QT-prolonging effect
84 occurred within 3 hours. The QT interval should be monitored when POTIGA is prescribed with
85 medicines known to increase QT interval and in patients with known prolonged QT interval,
86 congestive heart failure, ventricular hypertrophy, hypokalemia, or hypomagnesemia [*see Clinical*
87 *Pharmacology (12.2)*].

88 **5.5 Suicidal Behavior and Ideation**

89 Antiepileptic drugs (AEDs), including POTIGA, increase the risk of suicidal thoughts or
90 behavior in patients taking these drugs for any indication. Patients treated with any AED for any
91 indication should be monitored for the emergence or worsening of depression, suicidal thoughts
92 or behavior, and/or any unusual changes in mood or behavior.

93 Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive-therapy)
94 of 11 different AEDs showed that patients randomized to one of the AEDs had approximately
95 twice the risk (adjusted relative risk 1.8, 95% confidence interval [CI]: 1.2, 2.7) of suicidal
96 thinking or behavior compared to patients randomized to placebo. In these trials, which had a
97 median treatment duration of 12 weeks, the estimated incidence of suicidal behavior or ideation
98 among 27,863 AED-treated patients was 0.43% compared to 0.24% among 16,029 placebo-
99 treated patients, representing an increase of approximately 1 case of suicidal thinking or behavior
100 for every 530 patients treated. There were 4 suicides in drug-treated patients in the trials and
101 none in placebo-treated patients, but the number is too small to allow any conclusion about drug
102 effect on suicide.

103 The increased risk of suicidal thoughts or behavior with AEDs was observed as early as 1
104 week after starting treatment with AEDs and persisted for the duration of treatment assessed.
105 Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal
106 thoughts or behavior beyond 24 weeks could not be assessed.

107 The risk of suicidal thoughts or behavior was generally consistent among drugs in the
108 data analyzed. The finding of increased risk with AEDs of varying mechanism of action and
109 across a range of indications suggests that the risk applies to all AEDs used for any indication.
110 The risk did not vary substantially by age (5 to 100 years) in the clinical trials analyzed.

111 Table 3 shows absolute and relative risk by indication for all evaluated AEDs.

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Table 3. Risk of Suicidal Thoughts or Behaviors by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients With Events per 1,000 Patients	Drug Patients With Events per 1,000 Patients	Relative Risk: Incidence of Events in Drug Patients/ Incidence in Placebo Patients	Risk Difference: Additional Drug Patients With Events per 1,000 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

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

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

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Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression; any unusual changes in mood or behavior; or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

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5.6 Withdrawal Seizures

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As with all AEDs, when POTIGA is discontinued, it should be withdrawn gradually when possible to minimize the potential of increased seizure frequency [see *Dosage and Administration (2)*]. The dosage of POTIGA should be reduced over a period of at least 3 weeks, unless safety concerns require abrupt withdrawal.

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6 ADVERSE REACTIONS

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The following adverse reactions are described in more detail in the *Warnings and Precautions* section of the label:

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- Urinary retention [see *Warnings and Precautions (5.1)*]
- Neuro-psychiatric symptoms [see *Warnings and Precautions (5.2)*]
- Dizziness and somnolence [see *Warnings and Precautions (5.3)*]

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- 141 • QT interval effect [see Warnings and Precautions (5.4)]
- 142 • Suicidal behavior and ideation [see Warnings and Precautions (5.5)]
- 143 • Withdrawal seizures [see Warnings and Precautions (5.6)]

144 **6.1 Clinical Trials Experience**

145 Because clinical trials are conducted under widely varying conditions and for varying
146 durations, adverse reaction frequencies observed in the clinical trials of a drug cannot be directly
147 compared with frequencies in the clinical trials of another drug and may not reflect the
148 frequencies observed in practice.

149 POTIGA was administered as adjunctive therapy to 1,365 patients with epilepsy in all
150 controlled and uncontrolled clinical studies during the premarketing development. A total of 801
151 patients were treated for at least 6 months, 585 patients were treated for 1 year or longer, and 311
152 patients were treated for at least 2 years.

153 **Adverse Reactions Leading to Discontinuation in All Controlled Clinical Studies:**

154 In the 3 randomized, double-blind, placebo-controlled studies, 199 of 813 patients (25%)
155 receiving POTIGA and 45 of 427 patients (11%) receiving placebo discontinued treatment
156 because of adverse reactions. The most common adverse reactions leading to withdrawal in
157 patients receiving POTIGA were dizziness (6%), confusional state (4%), fatigue (3%), and
158 somnolence (3%).

159 **Common Adverse Reactions in All Controlled Clinical Studies:** Overall, the most
160 frequently reported adverse reactions in patients receiving POTIGA ($\geq 4\%$ and occurring
161 approximately twice the placebo rate) were dizziness (23%), somnolence (22%), fatigue (15%),
162 confusional state (9%), vertigo (8%), tremor (8%), abnormal coordination (7%), diplopia (7%),
163 disturbance in attention (6%), memory impairment (6%), asthenia (5%), blurred vision (5%), gait
164 disturbance (4%), aphasia (4%), dysarthria (4%), and balance disorder (4%). In most cases the
165 reactions were of mild or moderate intensity.

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167 **Table 4. Adverse Reaction Incidence in Placebo-Controlled Adjunctive Trials in Adult**
168 **Patients With Partial Onset Seizures (Adverse reactions in at least 2% of patients treated**
169 **with POTIGA in any treatment group and numerically more frequent than in the placebo**
170 **group.)**

Body System/ Adverse Reaction	Placebo (N = 427) %	POTIGA			
		600 mg/day (N = 281) %	900 mg/day (N = 273) %	1,200 mg/day (N = 259) %	All (N = 813) %
		Eye			
Diplopia	2	8	6	7	7
Blurred vision	2	2	4	10	5

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Gastrointestinal					
Nausea	5	6	6	9	7
Constipation	1	1	4	5	3
Dyspepsia	2	3	2	3	2
General					
Fatigue	6	16	15	13	15
Asthenia	2	4	6	4	5
Infections and infestations					
Influenza	2	4	1	5	3
Investigations					
Weight increased	1	2	3	3	3
Nervous system					
Dizziness	9	15	23	32	23
Somnolence	12	15	25	27	22
Memory impairment	3	3	6	9	6
Tremor	3	3	10	12	8
Vertigo	2	8	8	9	8
Abnormal coordination	3	5	5	12	7
Disturbance in attention	<1	6	6	7	6
Gait disturbance	1	2	5	6	4
Aphasia	<1	1	3	7	4
Dysarthria	<1	4	2	8	4
Balance disorder	<1	3	3	5	4
Paresthesia	2	3	2	5	3
Amnesia	<1	<1	3	3	2
Dysphasia	<1	1	1	3	2
Psychiatric					
Confusional state	3	4	8	16	9
Anxiety	2	3	2	5	3
Disorientation	<1	<1	<1	5	2
Psychotic disorder	0	0	<1	2	<1
Renal and urinary					
Dysuria	<1	1	2	4	2
Urinary hesitation	<1	2	1	4	2
Hematuria	<1	2	1	2	2
Chromaturia	<1	<1	2	3	2

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Other adverse reactions reported in these 3 studies in <2% of patients treated with POTIGA and numerically greater than placebo were increased appetite, hallucinations,

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174 myoclonus, peripheral edema, hypokinesia, dry mouth, dysphagia, hyperhydrosis, urinary
175 retention, malaise, and increased liver enzymes.

176 Most of the adverse reactions appear to be dose related (especially those classified as
177 psychiatric and nervous system symptoms), including dizziness, somnolence, confusional state,
178 tremor, abnormal coordination, memory impairment, blurred vision, gait disturbance, aphasia,
179 balance disorder, constipation, dysuria, and chromaturia.

180 POTIGA was associated with dose-related weight gain, with mean weight increasing by
181 0.2 kg, 1.2 kg, 1.6 kg, and 2.7 kg in the placebo, 600 mg per day, 900 mg per day, and 1,200 mg
182 per day groups, respectively.

183 Additional Adverse Reactions Observed During All Phase 2 and 3 Clinical Trials:

184 Following is a list of adverse reactions reported by patients treated with POTIGA during all
185 clinical trials: rash, nystagmus, dyspnea, leukopenia, muscle spasms, alopecia, nephrolithiasis,
186 syncope, neutropenia, thrombocytopenia, euphoric mood, renal colic, coma, encephalopathy.

187 Comparison of Gender, Age, and Race: The overall adverse reaction profile of
188 POTIGA was similar for females and males.

189 There are insufficient data to support meaningful analyses of adverse reactions by age or
190 race. Approximately 86% of the population studied was Caucasian, and 0.8% of the population
191 was older than 65 years.

192 **7 DRUG INTERACTIONS**

193 **7.1 Antiepileptic Drugs**

194 The potentially significant interactions between POTIGA and concomitant AEDs are
195 summarized in Table 5.

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197 **Table 5. Significant Interactions Between POTIGA and Concomitant Antiepileptic Drugs**

AED	Dose of AED (mg/day)	Dose of POTIGA (mg/day)	Influence of POTIGA on AED	Influence of AED on POTIGA	Dosage Adjustment
Carbamazepine ^{a,b}	600-2,400	300-1,200	None	31% decrease in AUC, 23% decrease in C _{max}	consider an increase in dosage of POTIGA when adding carbamazepine ^c
Phenytoin ^{a,b}	120-600	300-1,200	None	34% decrease in AUC, 18% decrease in C _{max}	consider an increase in dosage of POTIGA when adding phenytoin ^c

198 ^a Based on results of a Phase 2 study.

199 ^b Inducer for uridine 5'-diphosphate (UDP)-glucuronyltransferases (UGTs).

200 ^c A decrease in dosage of POTIGA should be considered when carbamazepine or phenytoin is
201 discontinued.

202 [See *Clinical Pharmacology (12.3)*]

203

204 **7.2 Digoxin**

205 Data from an *in vitro* study showed that the N-acetyl metabolite of ezogabine (NAMR)
206 inhibited P-glycoprotein-mediated transport of digoxin in a concentration-dependent manner,
207 indicating that NAMR may inhibit renal clearance of digoxin. Administration of POTIGA at
208 therapeutic doses may increase digoxin serum concentrations. Serum levels of digoxin should be
209 monitored [see *Clinical Pharmacology (12.3)*].

210 **7.3 Alcohol**

211 Alcohol increased systemic exposure to POTIGA. Patients should be advised of possible
212 worsening of ezogabine's general dose-related adverse reactions if they take POTIGA with
213 alcohol [see *Clinical Pharmacology (12.3)*].

214 **7.4 Laboratory Tests**

215 Ezogabine has been shown to interfere with clinical laboratory assays of both serum and
216 urine bilirubin, which can result in falsely elevated readings.

217 **8 USE IN SPECIFIC POPULATIONS**

218 **8.1 Pregnancy**

219 Pregnancy Category C. There are no adequate and well-controlled studies in pregnant
220 women. POTIGA should be used during pregnancy only if the potential benefit justifies the
221 potential risk to the fetus.

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222 In animal studies, doses associated with maternal plasma exposures (AUC) to ezogabine
223 and its major circulating metabolite, NAMR, similar to or below those expected in humans at the
224 maximum recommended human dose (MRHD) of 1,200 mg per day produced developmental
225 toxicity when administered to pregnant rats and rabbits. The maximum doses evaluated were
226 limited by maternal toxicity (acute neurotoxicity).

227 Treatment of pregnant rats with ezogabine (oral doses of up to 46 mg/kg/day) throughout
228 organogenesis increased the incidences of fetal skeletal variations. The no-effect dose for
229 embryo-fetal toxicity in rats (21 mg/kg/day) was associated with maternal plasma exposures
230 (AUC) to ezogabine and NAMR less than those in humans at the MRHD. Treatment of pregnant
231 rabbits with ezogabine (oral doses of up to 60 mg/kg/day) throughout organogenesis resulted in
232 decreased fetal body weights and increased incidences of fetal skeletal variations. The no-effect
233 dose for embryo-fetal toxicity in rabbits (12 mg/kg/day) was associated with maternal plasma
234 exposures to ezogabine and NAMR less than those in humans at the MRHD.

235 Administration of ezogabine (oral doses of up to 61.9 mg/kg/day) to rats throughout
236 pregnancy and lactation resulted in increased pre- and postnatal mortality, decreased body
237 weight gain, and delayed reflex development in the offspring. The no-effect dose for pre- and
238 postnatal developmental effects in rats (17.8 mg/kg/day) was associated with maternal plasma
239 exposures to ezogabine and NAMR less than those in humans at the MRHD.

240 **Pregnancy Registry:** To provide information regarding the effects of *in utero* exposure
241 to POTIGA, physicians are advised to recommend that pregnant patients taking POTIGA enroll
242 in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by
243 calling the toll-free number 1-888-233-2334, and must be done by patients themselves.
244 Information on the registry can also be found at the website www.aedpregnancyregistry.org.

245 **8.2 Labor and Delivery**

246 The effects of POTIGA on labor and delivery in humans are unknown.

247 **8.3 Nursing Mothers**

248 It is not known whether ezogabine is excreted in human milk. However, ezogabine and/or
249 its metabolites are present in the milk of lactating rats. Because of the potential for serious
250 adverse reactions in nursing infants from POTIGA, a decision should be made whether to
251 discontinue nursing or to discontinue the drug, taking into account the importance of the drug to
252 the mother.

253 **8.4 Pediatric Use**

254 The safety and effectiveness of POTIGA in patients under 18 years of age have not been
255 established.

256 In juvenile animal studies, increased sensitivity to acute neurotoxicity and urinary bladder
257 toxicity was observed in young rats compared to adults. In studies in which rats were dosed
258 starting on postnatal day 7, ezogabine-related mortality, clinical signs of neurotoxicity, and renal
259 and urinary tract toxicities were observed at doses ≥ 2 mg/kg/day. The no-effect level was
260 associated with plasma ezogabine exposures (AUC) less than those expected in human adults at

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261 the MRHD of 1,200 mg per day. In studies in which dosing began on postnatal day 28, acute
262 central nervous system effects, but no apparent renal or urinary tract effects, were observed at
263 doses of up to 30 mg/kg/day. These doses were associated with plasma ezogabine exposures less
264 than those achieved clinically at the MRHD.

265 **8.5 Geriatric Use**

266 There were insufficient numbers of elderly patients enrolled in partial-onset seizure
267 controlled trials (n = 8 patients on ezogabine) to determine the safety and efficacy of POTIGA in
268 this population. Dosage adjustment is recommended in patients aged 65 years and older [*see*
269 *Dosage and Administration (2), Clinical Pharmacology (12.3)*].

270 POTIGA may cause urinary retention. Elderly men with symptomatic BPH may be at
271 increased risk for urinary retention.

272 **8.6 Patients With Renal Impairment**

273 Dosage adjustment is recommended for patients with creatinine clearance <50 mL/min or
274 patients with end-stage renal disease (ESRD) receiving dialysis treatments [*see Dosage and*
275 *Administration (2), Clinical Pharmacology (12.3)*].

276 **8.7 Patients With Hepatic Impairment**

277 No dosage adjustment is required for patients with mild hepatic impairment.

278 In patients with moderate or severe hepatic impairment, the initial and maintenance
279 dosage of POTIGA should be reduced [*see Dosage and Administration (2), Clinical*
280 *Pharmacology (12.3)*].

281 **9 DRUG ABUSE AND DEPENDENCE**

282 **9.1 Controlled Substance**

283 POTIGA is a Schedule V controlled substance.

284 **9.2 Abuse**

285 A human abuse potential study was conducted in recreational sedative-hypnotic abusers
286 (n = 36) in which single oral doses of ezogabine (300 mg [n = 33], 600 mg [n = 34], 900 mg
287 [n = 6]), the sedative-hypnotic alprazolam (1.5 mg and 3.0 mg), and placebo were administered.
288 Euphoria-type subjective responses to the 300-mg and 600-mg doses of ezogabine were
289 statistically different from placebo but statistically indistinguishable from those produced by
290 either dose of alprazolam. Adverse events reported following administration of single oral doses
291 of 300 mg, 600 mg, and 900 mg ezogabine given without titration included euphoric mood (18%,
292 21%, and 33%, respectively; 8% from placebo), hallucination (0%, 0%, and 17%, respectively;
293 0% from placebo) and somnolence (18%, 15%, and 67%, respectively; 15% from placebo).

294 In Phase 1 clinical studies, healthy individuals who received oral ezogabine (200 mg to
295 1,650 mg) reported euphoria (8.5%), feeling drunk (5.5%), hallucination (5.1%), disorientation
296 (1.7%), and feeling abnormal (1.5%).

297 In the 3 randomized, double-blind, placebo-controlled Phase 2 and 3 clinical studies,
298 patients with partial seizures who received oral ezogabine (300 mg to 1,200 mg) reported

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299 euphoric mood (0.5%) and feeling drunk (0.9%), while those who received placebo did not
300 report either adverse event (0%).

301 **9.3 Dependence**

302 In a 28-day physical dependence study in which rats received daily ezogabine
303 administration, abrupt drug discontinuation produced behavioral changes that included
304 piloerection, increases in high step gait, and tremors, compared to vehicle-treated animals. These
305 data show that ezogabine produces a withdrawal syndrome indicative of physical dependence.

306 **10 OVERDOSAGE**

307 **10.1 Signs, Symptoms, and Laboratory Findings**

308 There is limited experience of overdose with POTIGA. Total daily doses of POTIGA
309 over 2,500 mg were reported during clinical trials. In addition to adverse reactions seen at
310 therapeutic doses, symptoms reported with POTIGA overdose included agitation, aggressive
311 behavior, and irritability. There were no reported sequelae.

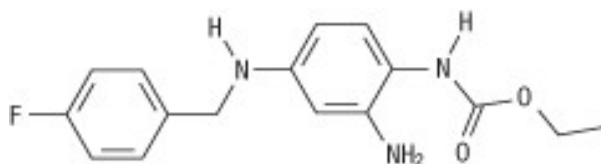
312 In an abuse potential study, cardiac arrhythmia (asystole or ventricular tachycardia)
313 occurred in 2 volunteers within 3 hours of receiving a single 900-mg dose of POTIGA. The
314 arrhythmias spontaneously resolved and both volunteers recovered without sequelae.

315 **10.2 Management of Overdose**

316 There is no specific antidote for overdose with POTIGA. In the event of overdose,
317 standard medical practice for the management of any overdose should be used. An adequate
318 airway, oxygenation, and ventilation should be ensured; monitoring of cardiac rhythm and vital
319 sign measurement is recommended. A certified poison control center should be contacted for
320 updated information on the management of overdose with POTIGA.

321 **11 DESCRIPTION**

322 The chemical name of ezogabine is N-[2-amino-4-(4-fluorobenzylamino)-phenyl]
323 carbamic acid ethyl ester, and it has the following structure:



324

325 The empirical formula is $C_{16}H_{18}FN_3O_2$, representing a molecular weight of 303.3.
326 Ezogabine is a white to slightly colored, odorless, tasteless, crystalline powder. At room
327 temperature, ezogabine is practically insoluble in aqueous media at pH values above 4, while the
328 solubility is higher in polar organic solvents. At gastric pH, ezogabine is sparingly soluble in
329 water (about 16 g/L). The pKa is approximately 3.7 (basic).

330 POTIGA is supplied for oral administration as 50-mg, 200-mg, 300-mg, and 400-mg
331 film-coated immediate-release tablets. Each tablet contains the labeled amount of ezogabine and
332 the following inactive ingredients: carmine (50-mg and 400-mg tablets), croscarmellose sodium,

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333 FD&C Blue No. 2 (50-mg, 300-mg, and 400-mg tablets), hypromellose, iron oxide yellow
334 (200-mg and 300-mg tablets), lecithin, magnesium stearate, microcrystalline cellulose, polyvinyl
335 alcohol, talc, titanium dioxide, and xanthan gum.

336 **12 CLINICAL PHARMACOLOGY**

337 **12.1 Mechanism of Action**

338 The mechanism by which ezogabine exerts its therapeutic effects has not been fully
339 elucidated. *In vitro* studies indicate that ezogabine enhances transmembrane potassium currents
340 mediated by the KCNQ (Kv7.2 to 7.5) family of ion channels. By activating KCNQ channels,
341 ezogabine is thought to stabilize the resting membrane potential and reduce brain excitability. *In*
342 *vitro* studies suggest that ezogabine may also exert therapeutic effects through augmentation of
343 GABA-mediated currents.

344 **12.2 Pharmacodynamics**

345 The QTc prolongation risk of POTIGA was evaluated in healthy subjects. In a
346 randomized, double-blind, active- and placebo-controlled parallel-group study, 120 healthy
347 subjects (40 in each group) were administered POTIGA titrated up to the final dose of 400 mg 3
348 times daily, placebo, and placebo and moxifloxacin (on day 22). After 22 days of dosing, the
349 maximum mean (upper 1-sided, 95% CI) increase of baseline- and placebo-adjusted QTc interval
350 based on Fridericia correction method (QTcF) was 7.7 msec (11.9 msec) and was observed at 3
351 hours after dosing in subjects who achieved 1,200 mg per day. No effects on heart rate, PR, or
352 QRS intervals were noted.

353 Patients who are prescribed POTIGA with medicines known to increase QT interval or
354 who have known prolonged QT interval, congestive heart failure, ventricular hypertrophy,
355 hypokalemia, or hypomagnesemia should be observed closely [*see Warnings and Precautions*
356 (5.4)].

357 **12.3 Pharmacokinetics**

358 The pharmacokinetic profile is approximately linear in daily doses between 600 mg and
359 1,200 mg in patients with epilepsy, with no unexpected accumulation following repeated
360 administration. The pharmacokinetics of ezogabine are similar in healthy volunteers and patients
361 with epilepsy.

362 **Absorption:** After both single and multiple oral doses, ezogabine is rapidly absorbed
363 with median time to maximum plasma concentration (T_{max}) values generally between 0.5 and 2
364 hours. Absolute oral bioavailability of ezogabine relative to an intravenous dose of ezogabine is
365 approximately 60%. High-fat food does not affect the extent to which ezogabine is absorbed
366 based on plasma AUC values, but it increases peak concentration (C_{max}) by approximately 38%
367 and delays T_{max} by 0.75 hour.

368 POTIGA can be taken with or without food.

369 **Distribution:** Data from *in vitro* studies indicate that ezogabine and NAMR are
370 approximately 80% and 45% bound to plasma protein, respectively. Clinically significant
371 interactions with other drugs through displacement from proteins are not anticipated. The steady-

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372 state volume of distribution of ezogabine is 2 to 3 L/kg following intravenous dosing, suggesting
373 that ezogabine is well distributed in the body.

374 **Metabolism:** Ezogabine is extensively metabolized primarily via glucuronidation and
375 acetylation in humans. A substantial fraction of the ezogabine dose is converted to inactive N-
376 glucuronides, the predominant circulating metabolites in humans. Ezogabine is also metabolized
377 to NAMR that is also subsequently glucuronidated. NAMR has antiepileptic activity, but it is
378 less potent than ezogabine in animal seizure models. Additional minor metabolites of ezogabine
379 are an N-glucoside of ezogabine and a cyclized metabolite believed to be formed from NAMR.
380 *In vitro* studies using human biomaterials showed that the N-acetylation of ezogabine was
381 primarily carried out by NAT2, while glucuronidation was primarily carried out by UGT1A4,
382 with contributions by UGT1A1, UGT1A3, and UGT1A9.

383 *In vitro* studies showed no evidence of oxidative metabolism of ezogabine or NAMR by
384 cytochrome P450 enzymes. Coadministration of ezogabine with medications that are inhibitors
385 or inducers of cytochrome P450 enzymes is therefore unlikely to affect the pharmacokinetics of
386 ezogabine or NAMR.

387 **Elimination:** Results of a mass balance study suggest that renal excretion is the major
388 route of elimination for ezogabine and NAMR. About 85% of the dose was recovered in the
389 urine, with the unchanged parent drug and NAMR accounting for 36% and 18% of the
390 administered dose, respectively, and the total N-glucuronides of ezogabine and NAMR
391 accounting for 24% of the administered dose. Approximately 14% of the radioactivity was
392 recovered in the feces, with unchanged ezogabine accounting for 3% of the total dose. Average
393 total recovery in both urine and feces within 240 hours after dosing is approximately 98%.

394 Ezogabine and its N-acetyl metabolite have similar elimination half-lives ($t_{1/2}$) of 7 to 11
395 hours. The clearance of ezogabine following intravenous dosing was approximately 0.4 to
396 0.6 L/hr/kg. Ezogabine is actively secreted into the urine.

397 **Specific Populations: Race:** No study has been conducted to investigate the impact of
398 race on pharmacokinetics of ezogabine. A population pharmacokinetic analysis comparing
399 Caucasians and non-Caucasians (predominately African American and Hispanic patients)
400 showed no significant pharmacokinetic difference. No adjustment of the ezogabine dose for race
401 is recommended.

402 **Gender:** The impact of gender on the pharmacokinetics of ezogabine was examined
403 following a single dose of POTIGA to healthy young (aged 21 to 40 years) and elderly (aged 66
404 to 82 years) subjects. The AUC values were approximately 20% higher in young females
405 compared to young males and approximately 30% higher in elderly females compared to elderly
406 males. The C_{max} values were approximately 50% higher in young females compared to young
407 males and approximately 100% higher in elderly females compared to elderly males. There was
408 no gender difference in weight-normalized clearance. Overall, no adjustment of the dosage of
409 POTIGA is recommended based on gender.

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410 **Pediatric Patients:** The pharmacokinetics of ezogabine in pediatric patients have not
411 been investigated.

412 **Geriatric:** The impact of age on the pharmacokinetics of ezogabine was examined
413 following a single dose of ezogabine to healthy young (aged 21 to 40 years) and elderly (aged 66
414 to 82 years) subjects. Systemic exposure (AUC) of ezogabine was approximately 40% to 50%
415 higher and terminal half-life was prolonged by approximately 30% in the elderly compared to the
416 younger subjects. The peak concentration (C_{max}) was similar to that observed in younger
417 subjects. A dosage reduction in the elderly is recommended [*see Dosage and Administration (2),*
418 *Use in Specific Populations (8.5)*].

419 **Renal Impairment:** The pharmacokinetics of ezogabine were studied following a
420 single 100-mg dose of POTIGA in subjects with normal ($CrCL >80$ mL/min), mild ($CrCL \geq 50$ to
421 <80 mL/min), moderate ($CrCL \geq 30$ to <50 mL/min), or severe renal impairment ($CrCL <30$
422 mL/min) ($n = 6$ in each cohort) and in subjects with ESRD requiring hemodialysis ($n = 6$). The
423 ezogabine AUC was increased by approximately 30% in patients with mild renal impairment and
424 doubled in patients with moderate impairment to ESRD ($CrCL <50$ mL/min) relative to healthy
425 subjects. Similar increases in NAMR exposure were observed in the various degrees of renal
426 impairment. The effect of hemodialysis on ezogabine clearance has not been established. Dosage
427 reduction is recommended for patients with creatinine clearance <50 mL/min and for patients
428 with ESRD receiving dialysis [*see Dosage and Administration (2), Use in Specific Populations*
429 *(8.6)*].

430 **Hepatic Impairment:** The pharmacokinetics of ezogabine were studied following a
431 single 100-mg dose of POTIGA in subjects with normal, mild (Child-Pugh score 5 to 6),
432 moderate (Child-Pugh score 7 to 9), or severe hepatic (Child-Pugh score >9) impairment ($n = 6$
433 in each cohort). Relative to healthy subjects, ezogabine AUC was not affected by mild hepatic
434 impairment, but was increased by approximately 50% in subjects with moderate hepatic
435 impairment and doubled in subjects with severe hepatic impairment. There was an increase of
436 approximately 30% in exposure to NAMR in patients with moderate to severe impairment.
437 Dosage reduction is recommended for patients with moderate and severe hepatic impairment
438 [*see Dosage and Administration (2), Use in Specific Populations (8.7)*].

439 **Drug Interactions:** *In vitro* studies using human liver microsomes indicated that
440 ezogabine does not inhibit enzyme activity for CYP1A2, CYP2A6, CYP2C8, CYP2C9,
441 CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5. Inhibition of CYP2B6 by ezogabine has not
442 been evaluated. In addition, *in vitro* studies in human primary hepatocytes showed that
443 ezogabine and NAMR did not induce CYP1A2 or CYP3A4/5 activity. Therefore, ezogabine is
444 unlikely to affect the pharmacokinetics of substrates of the major cytochrome P450 isoenzymes
445 through inhibition or induction mechanisms.

446 Ezogabine is neither a substrate nor an inhibitor of P-glycoprotein, an efflux transporter.
447 NAMR is a P-glycoprotein inhibitor. Data from an *in vitro* study showed that NAMR inhibited
448 P-glycoprotein-mediated transport of digoxin in a concentration-dependent manner, indicating

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449 that NAMR may inhibit renal clearance of digoxin. Administration of POTIGA at therapeutic
450 doses may increase digoxin serum concentrations [see *Drug Interactions (7.2)*].

451 *Interactions with Antiepileptic Drugs:* The interactions between POTIGA and
452 concomitant AEDs are summarized in Table 6.

453

454 **Table 6. Interactions Between POTIGA and Concomitant Antiepileptic Drugs**

AED	Dose of AED (mg/day)	Dose of POTIGA (mg/day)	Influence of POTIGA on AED	Influence of AED on POTIGA	Dosage Adjustment
Carbamazepine ^{a,b}	600-2,400	300-1,200	None	31% decrease in AUC, 23% decrease in C _{max} , 28% increase in clearance	consider an increase in dosage of POTIGA when adding carbamazepine ^c
Phenytoin ^{a,b}	120-600	300-1,200	None	34% decrease in AUC, 18% decrease in C _{max} , 33% increase in clearance	consider an increase in dosage of POTIGA when adding phenytoin ^c
Topiramate ^a	250-1,200	300-1,200	None	None	None
Valproate ^a	750-2,250	300-1,200	None	None	None
Phenobarbital	90	600	None	None	None
Lamotrigine	200	600	18% decrease in AUC, 22% increase in clearance	None	None
Others ^d			None	None	None

455 ^a Based on results of a Phase 2 study.

456 ^b Inducer for uridine 5'-diphosphate (UDP)-glucuronyltransferases (UGTs).

457 ^c A decrease in dose of POTIGA should be considered when carbamazepine or phenytoin is
458 discontinued.

459 ^d Zonisamide, valproic acid, clonazepam, gabapentin, levetiracetam, oxcarbazepine,
460 phenobarbital, pregabalin, topiramate, clobazam, and lamotrigine, based on a population
461 pharmacokinetic analysis using pooled data from Phase 3 clinical trials.

462

463 *Oral Contraceptives:* In one study examining the potential interaction between
464 ezogabine (150 mg 3 times daily for 3 days) and the combination oral contraceptive
465 norgestrel/ethinyl estradiol (0.3 mg/0.03 mg) tablets in 20 healthy females, no significant
466 alteration in the pharmacokinetics of either drug was observed.

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467 In a second study examining the potential interaction of repeated ezogabine dosing
468 (250 mg 3 times daily for 14 days) and the combination oral contraceptive norethindrone/ethinyl
469 estradiol (1 mg/0.035 mg) tablets in 25 healthy females, no significant alteration in the
470 pharmacokinetics of either drug was observed.

471 *Alcohol:* In a healthy volunteer study, the coadministration of ethanol 1g/kg (5
472 standard alcohol drinks) over 20 minutes and ezogabine (200 mg) resulted in an increase in the
473 ezogabine C_{max} and AUC by 23% and 37%, respectively [see *Drug Interactions (7.3)*].

474 **13 NONCLINICAL TOXICOLOGY**

475 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

476 Carcinogenesis: In a one-year neonatal mouse study of ezogabine (2 single-dose oral
477 administrations of up to 96 mg/kg on postnatal days 8 and 15), a dose-related increase in the
478 frequency of lung neoplasms (bronchioalveolar carcinoma and/or adenoma) was observed in
479 treated males. No evidence of carcinogenicity was observed in rats following oral administration
480 of ezogabine (oral gavage doses of up to 50 mg/kg/day) for 2 years. Plasma exposure (AUC) to
481 ezogabine at the highest doses tested was less than that in humans at the maximum
482 recommended human dose (MRHD) of 1,200 mg per day.

483 Mutagenesis: Highly purified ezogabine was negative in the *in vitro* Ames assay, the *in*
484 *vitro* Chinese hamster ovary (CHO) *Hprt* gene mutation assay, and the *in vivo* mouse
485 micronucleus assay. Ezogabine was positive in the *in vitro* chromosomal aberration assay in
486 human lymphocytes. The major circulating metabolite of ezogabine, NAMR, was negative in the
487 *in vitro* Ames assay, but positive in the *in vitro* chromosomal aberration assay in CHO cells.

488 Impairment of Fertility: Ezogabine had no effect on fertility, general reproductive
489 performance, or early embryonic development when administered to male and female rats at
490 doses of up to 46.4 mg/kg/day (associated with a plasma ezogabine exposure [AUC] less than
491 that in humans at the MRHD) prior to and during mating, and continuing in females through
492 gestation day 7.

493 **14 CLINICAL STUDIES**

494 The efficacy of POTIGA as adjunctive therapy in partial-onset seizures was established
495 in 3 multicenter, randomized, double-blind, placebo-controlled studies in 1,239 adult patients.
496 The primary endpoint consisted of the percent change in seizure frequency from baseline in the
497 double-blind treatment phase.

498 Patients enrolled in the studies had partial onset seizures with or without secondary
499 generalization and were not adequately controlled with 1 to 3 concomitant AEDs, with or
500 without concomitant vagus nerve stimulation. More than 75% of patients were taking 2 or more
501 concomitant AEDs. During an 8-week baseline period, patients experienced at least 4 partial
502 onset seizures per 28 days on average with no seizure-free period exceeding 3 to 4 weeks.
503 Patients had a mean duration of epilepsy of 22 years. Across the 3 studies, the median baseline

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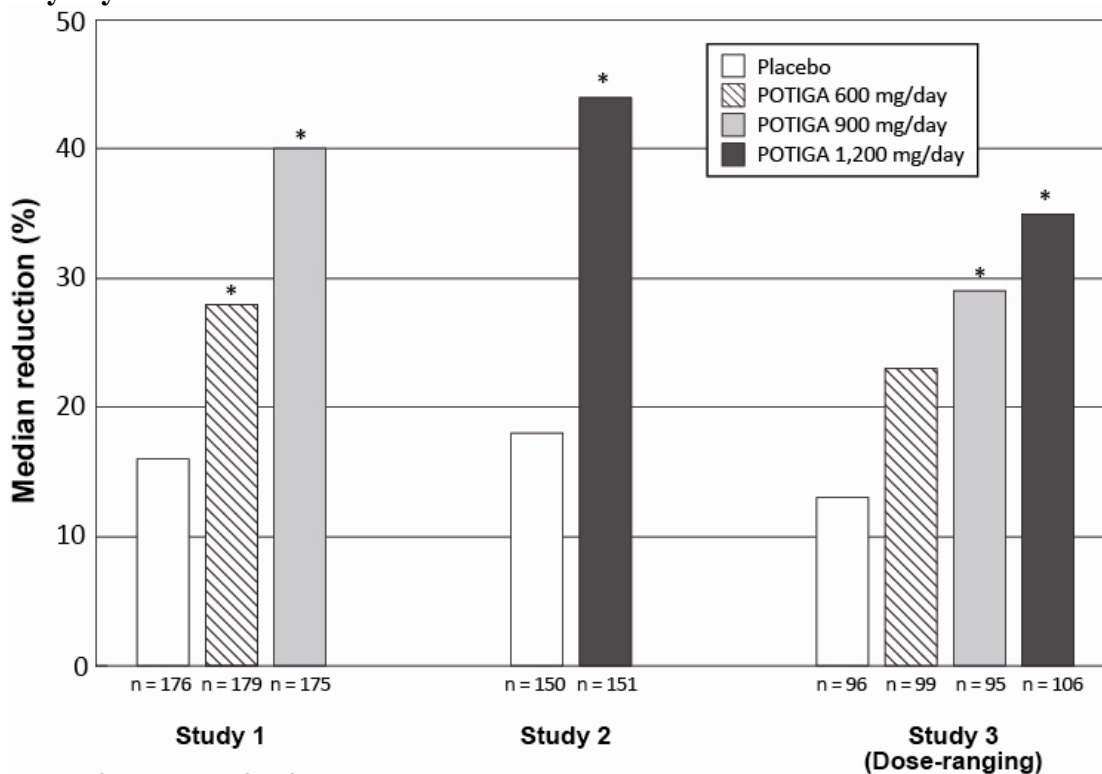
504 seizure frequency ranged from 8 to 12 seizures per month. The criteria for statistical significance
 505 was $P < 0.05$.

506 Patients were randomized to the total daily maintenance dosages of 600 mg per day,
 507 900 mg per day, or 1,200 mg per day, each administered in 3 equally divided doses. During the
 508 titration phase of all 3 studies, treatment was initiated at 300 mg per day (100 mg 3 times per
 509 day) and increased in weekly increments of 150 mg per day to the target maintenance dosage.

510 Figure 1 shows the median percent reduction in 28-day seizure frequency (baseline to
 511 double-blind phase) as compared with placebo across all 3 studies. A statistically significant
 512 effect was observed with POTIGA at doses of 600 mg per day (Study 1), at 900 mg per day
 513 (Studies 1 and 3), and at 1,200 mg per day (Studies 2 and 3).

514

515 **Figure 1. Median Percent Reduction From Baseline in Seizure Frequency per 28**
 516 **Days by Dose**



517

518

519 Figure 2 shows changes from baseline in the 28-day total partial seizure frequency by
 520 category for patients treated with POTIGA and placebo in an integrated analysis across the 3
 521 clinical trials. Patients in whom the seizure frequency increased are shown at left as “worse.”
 522 Patients in whom the seizure frequency decreased are shown in five categories.

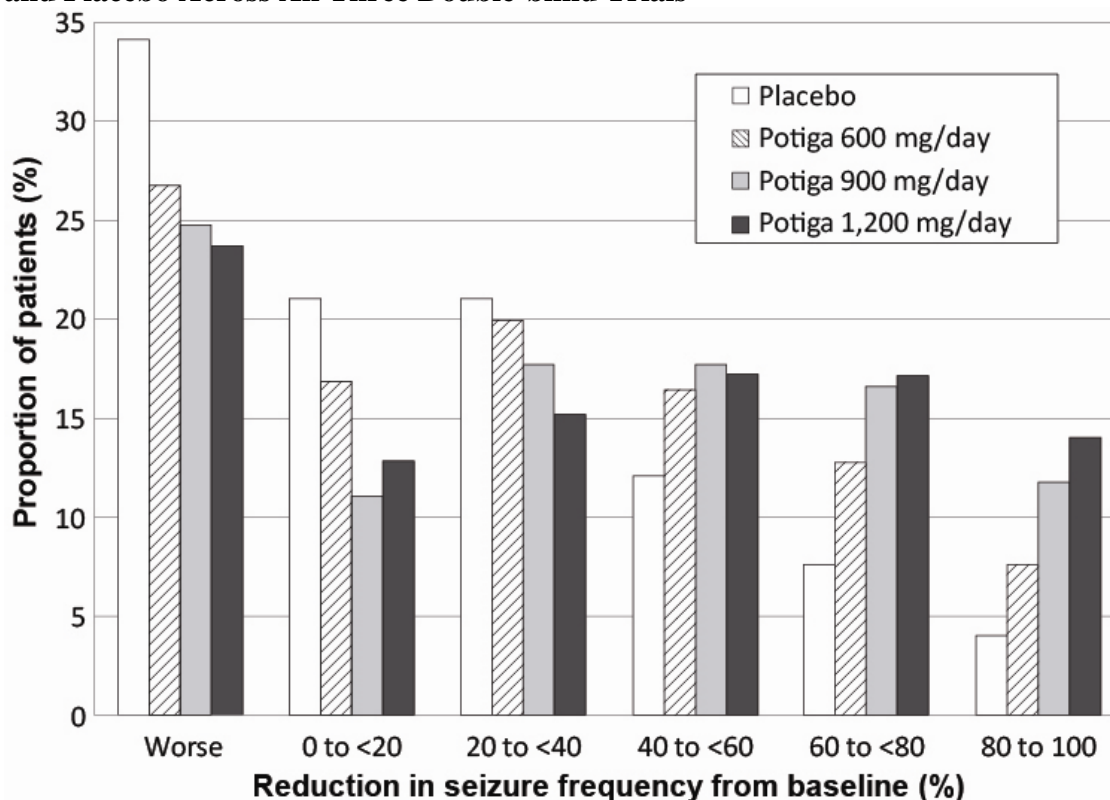
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524 **Figure 2. Proportion of Patients by Category of Seizure Response for POTIGA**
525 **and Placebo Across All Three Double-blind Trials**



526

527 **16 HOW SUPPLIED/STORAGE AND HANDLING**

528 POTIGA is supplied as film-coated immediate-release tablets for oral administration
529 containing 50 mg, 200 mg, 300 mg, or 400 mg of ezogabine in the following packs:

530 **50-mg Tablets:** purple, round, film-coated tablets debossed with “RTG 50” on one side in
531 bottles of 90 with desiccant (NDC 0173-0810-59).

532 **200-mg Tablets:** yellow, oblong, film-coated tablets debossed with “RTG-200” on one side in
533 bottles of 90 with desiccant (NDC 0173-0812-59).

534 **300-mg Tablets:** green, oblong, film-coated tablets debossed with “RTG-300” on one side in
535 bottles of 90 with desiccant (NDC 0173-0813-59).

536 **400-mg Tablets:** purple, oblong, film-coated tablets debossed with “RTG-400” on one side in
537 bottles of 90 with desiccant (NDC 0173-0814-59).

538 Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [See USP Controlled
539 Room Temperature.]

540 **17 PATIENT COUNSELING INFORMATION**

541 See FDA-approved patient labeling (Medication Guide).

542 **17.1 Urinary Retention**

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543 Patients should be informed that POTIGA can cause urinary retention (including urinary
544 hesitation and dysuria). If patients experience any symptoms of urinary retention, inability to
545 urinate, and/or pain with urination, they should be instructed to seek immediate medical
546 assistance [see *Warnings and Precautions (5.1)*]. For patients who cannot reliably report
547 symptoms of urinary retention (for example, patients with cognitive impairment), urologic
548 consultation may be helpful.

549 **17.2 Psychiatric Symptoms**

550 Patients should be informed that POTIGA can cause psychiatric symptoms such as
551 confusional state, disorientation, hallucinations, and other symptoms of psychosis. Patients and
552 their caregivers should be instructed to notify their physicians if they experience psychotic
553 symptoms [see *Warnings and Precautions (5.2)*].

554 **17.3 Central Nervous System Effects**

555 Patients should be informed that POTIGA may cause dizziness, somnolence, memory
556 impairment, abnormal coordination/balance, disturbance in attention, and ophthalmological
557 effects such as diplopia or blurred vision. Patients taking POTIGA should be advised not to
558 drive, operate complex machinery, or engage in other hazardous activities until they have
559 become accustomed to any such effects associated with POTIGA [see *Warnings and Precautions*
560 *(5.3)*].

561 **17.4 Suicidal Thinking and Behavior**

562 Patients, their caregivers, and families should be informed that AEDs, including
563 POTIGA, may increase the risk of suicidal thoughts and behavior and should be advised of the
564 need to be alert for the emergence or worsening of symptoms of depression, any unusual changes
565 in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-
566 harm. Behaviors of concern should be reported immediately to healthcare providers [see
567 *Warnings and Precautions (5.5)*].

568 **17.5 Pregnancy**

569 Patients should be advised to notify their physicians if they become pregnant or intend to
570 become pregnant during therapy. Patients should be advised to notify their physicians if they
571 intend to breastfeed or are breastfeeding an infant.

572 Patients should be encouraged to enroll in the NAAED Pregnancy Registry if they
573 become pregnant. This registry collects information about the safety of AEDs during pregnancy.
574 To enroll, patients can call the toll-free number 1-888-233-2334 [see *Use in Specific Populations*
575 *(8.1)*].

576
577 POTIGA is a trademark of Valeant Pharmaceuticals North America.

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MEDICATION GUIDE
POTIGA™ (po-TEE-ga) Tablets, CV
(ezogabine)

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Read this Medication Guide before you start taking POTIGA and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment. If you have questions about POTIGA, ask your healthcare provider or pharmacist.

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What is the most important information I should know about POTIGA?

Do not stop POTIGA without first talking to a healthcare provider. Stopping POTIGA suddenly can cause serious problems. Stopping POTIGA suddenly can cause you to have more seizures more often.

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- 1. POTIGA can make it hard for you to urinate** (empty your bladder) and may cause you to be unable to urinate. Call your healthcare provider right away if you:
- are unable to start urinating
 - have trouble emptying your bladder
 - have a weak urine stream
 - have pain with urination

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- 2. POTIGA can cause mental (psychiatric) problems, including:**
- confusion
 - new or worse aggressive behavior, hostility, anger, or irritability
 - new or worse psychosis (hearing or seeing things that are not real)
 - being suspicious or distrustful (believing things that are not true)
 - other unusual or extreme changes in behavior or mood

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Tell your healthcare provider right away if you have any new or worsening mental problems while using POTIGA.

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616 **3. Like other antiepileptic drugs, POTIGA may cause suicidal thoughts or actions in a**
617 **very small number of people, about 1 in 500.**

618 **Call a healthcare provider right away if you have any of these symptoms, especially if**
619 **they are new, worse, or worry you:**

- 620 • thoughts about suicide or dying
- 621 • attempt to commit suicide
- 622 • new or worse depression
- 623 • new or worse anxiety
- 624 • feeling agitated or restless
- 625 • panic attacks
- 626 • trouble sleeping (insomnia)
- 627 • new or worse irritability
- 628 • acting aggressive, being angry, or violent
- 629 • acting on dangerous impulses
- 630 • an extreme increase in activity and talking (mania)
- 631 • other unusual changes in behavior or mood

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

634

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

- 636 • Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or
637 feelings.
- 638 • Keep all follow-up visits with your healthcare provider as scheduled.

639 Call your healthcare provider between visits as needed, especially if you are worried about
640 symptoms.

641 **Do not stop POTIGA without first talking to a healthcare provider.**

642 Stopping POTIGA suddenly can cause serious problems. Stopping POTIGA suddenly can cause
643 you to have more seizures more often.

644

645 **What is POTIGA?**

646 POTIGA is a prescription medicine that is used with other medicines to treat partial onset
647 seizures in people with epilepsy who are 18 years of age or older.

648 POTIGA is a controlled substance (CV) because it can be abused or lead to drug dependence.
649 Keep your POTIGA in a safe place to protect it from theft. Never give your POTIGA to anyone
650 else because it may harm them. Selling or giving away this medicine is against the law.

651

652 It is not known if POTIGA is safe and effective in children under 18 years of age.

653

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654 **What should I tell my healthcare provider before taking POTIGA?**

655 **Before you take POTIGA, tell your healthcare provider if you:**

- 656 • have trouble urinating
- 657 • have an enlarged prostate
- 658 • have or have had depression, mood problems, or suicidal thoughts or behavior
- 659 • have heart problems, including a condition called long QT Syndrome, or have low potassium
- 660 or magnesium in your blood
- 661 • have liver problems
- 662 • have kidney problems
- 663 • drink alcohol
- 664 • have any other medical conditions
- 665 • are pregnant or plan to become pregnant. It is not known if POTIGA will harm your unborn
- 666 baby.
- 667 • If you become pregnant while taking POTIGA, talk to your healthcare provider about
- 668 registering with the North American Antiepileptic Drug Pregnancy Registry. The purpose
- 669 of this registry is to collect information about the safety of medicines used to treat
- 670 seizures during pregnancy. You can enroll in this registry by calling 1-888-233-2334.
- 671 • are breastfeeding or plan to breastfeed. It is not known if POTIGA passes into your breast
- 672 milk. Talk to your healthcare provider about the best way to feed your baby if you take
- 673 POTIGA. You and your healthcare provider should decide if you will take POTIGA or
- 674 breastfeed. You should not do both.

675 **Tell your healthcare provider about all the medicines you take**, including prescription and

676 non-prescription medicines, vitamins, and herbal supplements. Taking POTIGA with certain

677 other medicines can affect each other, causing side effects. **Especially tell your healthcare**

678 **provider if you take:**

- 679 • digoxin (LANOXIN[®])
- 680 • phenytoin (DILANTIN[®], PHENYTEK[®])
- 681 • carbamazepine (CARBATROL[®], TEGRETOL[®], TEGRETOL[®]-XR, EQUETRO[®],
- 682 EPITOL[®])

683 Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you

684 get a new medicine.

- 685 • Take POTIGA exactly as your healthcare provider tells you to take it. Your healthcare
- 686 provider will tell you how much POTIGA to take and when to take it.
- 687 • Your healthcare provider may change your dose of POTIGA. Do not change your dose
- 688 without talking to your healthcare provider.
- 689 • POTIGA can be taken with or without food.
- 690 • Swallow POTIGA Tablets whole. Do not break, crush, dissolve, or chew POTIGA tablets
- 691 before swallowing.
- 692 • Talk to your doctor about what to do if you miss one or more doses of POTIGA.

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- 693 • If you take too much POTIGA, call your local Poison Control Center or go to the nearest
694 hospital emergency room right away.

695

696 **What should I avoid while taking POTIGA?**

697 Do not drive, operate machinery, or do other dangerous activities until you know how POTIGA
698 affects you. POTIGA can cause dizziness, sleepiness, double-vision, and blurred vision.

699

700 **What are the possible side effects of POTIGA?**

701 **POTIGA may cause serious side effects, including:**

- 702 • See “What is the most important information I should know about POTIGA?”
703 **Dizziness and sleepiness.** These symptoms can increase when your dose of POTIGA is
704 increased. See “What should I avoid while taking POTIGA?”
705 **Changes in your heart rhythm and the electrical activity of your heart.** Your healthcare
706 provider should monitor your heart during treatment if you have a certain type of heart
707 disease or take certain medications.
708 • Drinking alcohol during treatment with POTIGA may increase the side effects that you get
709 with POTIGA.

710 The most common side effects of POTIGA include:

- 711 • dizziness
712 • somnolence
713 • sleepiness
714 • tiredness
715 • confusion
716 • spinning sensation (vertigo)
717 • tremor
718 • problems with balance and muscle coordination, including trouble with walking and moving
719 • blurred or double vision
720 • trouble concentrating
721 • memory problems
722 • weakness

723 Tell your healthcare provider about any side effect that bothers you or that does not go away.

724 These are not all the possible side effects of POTIGA. Ask your healthcare provider or
725 pharmacist for more information.

726 Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-
727 800-FDA-1088.

728

729 **How should I store POTIGA?**

- 730 • Store POTIGA at room temperature at 59°F to 86°F (15°C to 30°C).

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731 • **Keep POTIGA and all medicines out of the reach of children.**

732

733 **General information about the safe and effective use of POTIGA.**

734 Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.

735 Do not use POTIGA for a condition for which it was not prescribed. Do not give POTIGA to
736 other people, even if they have the same symptoms you have. It may harm them.

737 This Medication Guide summarizes the most important information about POTIGA. If you
738 would like more information, talk with your healthcare provider. You can ask your healthcare
739 provider or pharmacist for information about POTIGA that is written for healthcare
740 professionals.

741 For more information, go to www.potiga.com or call 1-888-825-5249.

742

743 **What are the ingredients in POTIGA?**

744 Active ingredient: ezogabine.

745 Inactive ingredients in all strengths: croscarmellose sodium, hypromellose, lecithin, magnesium
746 stearate, microcrystalline cellulose, polyvinyl alcohol, talc, titanium dioxide, and xanthan gum.

747 50-mg and 400-mg tablets also contain: carmine.

748 50-mg, 300-mg, and 400-mg tablets also contain: FD&C Blue No 2.

749 200-mg and 300-mg tablets also contain: iron oxide yellow.

750

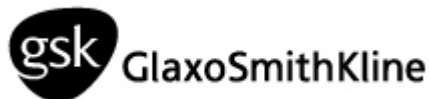
751 POTIGA is a trademark of Valeant Pharmaceuticals North America.

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754 GlaxoSmithKline. The makers of these brands are not affiliated with and do not endorse
755 GlaxoSmithKline or its products.

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

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