

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**

WARNING: RETINAL ABNORMALITIES AND POTENTIAL VISION LOSS

See full prescribing information for complete boxed warning.

- POTIGA can cause retinal abnormalities with funduscopy features similar to those seen in retinal pigment dystrophies, which are known to result in damage to the photoreceptors and vision loss.
- Some patients with retinal abnormalities have been found to have abnormal visual acuity. It is not possible to determine whether POTIGA caused this decreased visual acuity.
- The rate of progression of retinal abnormalities and their reversibility are unknown.
- Patients who fail to show substantial clinical benefit after adequate titration should be discontinued from POTIGA.
- All patients taking POTIGA should have baseline and periodic (every 6 months) systematic visual monitoring by an ophthalmic professional. Testing should include visual acuity and dilated fundus photography.
- If retinal pigmentary abnormalities or vision changes are detected, POTIGA should be discontinued unless no other suitable treatment options are available and the benefits of treatment outweigh the potential risk of vision loss.

- POTIGA may cause retinal abnormalities with long-term use; therefore, treatment should be discontinued if patients fail to show substantial clinical benefit after adequate titration. (2.2)
- Testing of visual function should be done at baseline and every 6 months during therapy with POTIGA (2.2).
- If retinal pigmentary abnormalities or vision changes are detected, POTIGA should be discontinued unless no other suitable treatment options are available and the benefits of treatment outweigh the potential risk of vision loss. (2.2)
- Dosing adjustments are required for geriatric patients and patients with moderate to severe renal or hepatic impairment. (2.3)

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. (5.2)
- POTIGA can cause skin discoloration: If a patient develops skin discoloration, serious consideration should be given to an alternative treatment. (5.3)
- Neuropsychiatric symptoms: Monitor for confusional state, psychotic symptoms, and hallucinations. (5.4)
- Dizziness and somnolence: Monitor for dizziness and somnolence. (5.5)
- QT prolongation: QT interval should be monitored in patients taking concomitant medications known to increase the QT interval or with certain heart conditions. (5.6)
- Suicidal behavior and ideation: Monitor for suicidal thoughts or behaviors. (5.7)

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥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: 09/2013

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

1 FULL PRESCRIBING INFORMATION

2 **WARNING: RETINAL ABNORMALITIES AND POTENTIAL VISION LOSS**

- 3 • **POTIGA can cause retinal abnormalities with fundusoscopic features similar to those**
- 4 **seen in retinal pigment dystrophies, which are known to result in damage to the**
- 5 **photoreceptors and vision loss.**
- 6 • **Some patients with retinal abnormalities have been found to have abnormal visual**
- 7 **acuity. It is not possible to determine whether POTIGA caused this decreased visual**
- 8 **acuity, as baseline assessments are not available for these patients.**
- 9 • **Approximately one third of the patients who had eye examinations performed after**
- 10 **approximately 4 years of treatment were found to have retinal pigmentary**
- 11 **abnormalities. An earlier onset cannot be ruled out, and it is possible that retinal**
- 12 **abnormalities were present earlier in the course of exposure to POTIGA. The rate of**
- 13 **progression of retinal abnormalities and their reversibility are unknown.**
- 14 • **POTIGA should only be used in patients who have responded inadequately to several**
- 15 **alternative treatments and for whom the benefits outweigh the potential risk of vision**
- 16 **loss. Patients who fail to show substantial clinical benefit after adequate titration should**
- 17 **be discontinued from POTIGA.**
- 18 • **All patients taking POTIGA should have baseline and periodic (every 6 months)**
- 19 **systematic visual monitoring by an ophthalmic professional. Testing should include**
- 20 **visual acuity and dilated fundus photography. Additional testing may include**
- 21 **fluorescein angiograms (FA), ocular coherence tomography (OCT), perimetry, and**
- 22 **electroretinograms (ERG).**

- 23 • **If retinal pigmentary abnormalities or vision changes are detected, POTIGA should be**
24 **discontinued unless no other suitable treatment options are available and the benefits of**
25 **treatment outweigh the potential risk of vision loss.**

26 **1 INDICATIONS AND USAGE**

27 POTIGA[®] is indicated as adjunctive treatment of partial-onset seizures in patients aged
28 18 years and older who have responded inadequately to several alternative treatments and for
29 whom the benefits outweigh the risk of retinal abnormalities and potential decline in visual
30 acuity [*see Warnings and Precautions (5.1)*].

31 **2 DOSAGE AND ADMINISTRATION**

32 **2.1 Dosing Information**

33 The initial dosage should be 100 mg 3 times daily (300 mg per day). The dosage should
34 be increased gradually at weekly intervals by no more than 50 mg 3 times daily (increase in the
35 daily dose of no more than 150 mg per day) up to a maintenance dosage of 200 mg to 400 mg 3
36 times daily (600 mg to 1,200 mg per day), based on individual patient response and tolerability.
37 This information is summarized in Table 1 under Dosing in Specific Populations. In the
38 controlled clinical trials, 400 mg 3 times daily showed limited evidence of additional
39 improvement in seizure reduction, but an increase in adverse events and discontinuations,
40 compared to the 300 mg 3 times daily dosage. The safety and efficacy of doses greater than
41 400 mg 3 times daily (1,200 mg per day) have not been examined in controlled trials.

42 POTIGA should be given orally in 3 equally divided doses daily, with or without food.
43 POTIGA Tablets should be swallowed whole.

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

46 **2.2 Dosing Considerations to Mitigate the Risk of Visual Adverse Reactions**

47 Because POTIGA may cause retinal abnormalities with long-term use, patients who fail
48 to show substantial clinical benefit after adequate titration should be discontinued from
49 POTIGA. Testing of visual function should be done at baseline and every 6 months during
50 therapy with POTIGA. Patients who cannot be monitored should usually not be treated with
51 POTIGA. If retinal pigmentary abnormalities or vision changes are detected, POTIGA should be
52 discontinued unless no other suitable treatment options are available and the benefits of
53 treatment outweigh the potential risk of vision loss [*see Warnings and Precautions (5.1)*].

54 **2.3 Dosing in Specific Populations**

55 No adjustment in dosage is required for patients with mild renal or hepatic impairment
56 (see Table 1). Dosage adjustment is required in geriatric and patients with moderate and greater
57 renal or hepatic impairment (see Table 1).

58

59 **Table 1. Dosing in Specific Populations**

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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61 **3 DOSAGE FORMS AND STRENGTHS**

- 62 50 mg, purple, round, film-coated tablets debossed with “RTG 50” on one side.
63 200 mg, yellow, oblong, film-coated tablets debossed with “RTG-200” on one side.
64 300 mg, green, oblong, film-coated tablets debossed with “RTG-300” on one side.
65 400 mg, purple, oblong, film-coated tablets debossed with “RTG-400” on one side.

66 **4 CONTRAINDICATIONS**

67 None.

68 **5 WARNINGS AND PRECAUTIONS**69 **5.1 Retinal Abnormalities and Potential Vision Loss**

70 POTIGA can cause abnormalities of the retina. The abnormalities seen in patients treated
71 with POTIGA have funduscopy features similar to those seen in retinal pigment dystrophies that
72 are known to result in damage to photoreceptors and vision loss.

73 The retinal abnormalities observed with POTIGA have been reported in patients who
74 were originally enrolled in clinical trials with POTIGA and who have generally taken the drug
75 for a long period of time in 2 ongoing extension studies. Approximately one third of the patients

76 who had eye examinations performed after approximately 4 years of treatment were found to
77 have retinal pigmentary abnormalities. However, an earlier onset cannot be ruled out, and it is
78 possible that retinal abnormalities were present earlier in the course of exposure to POTIGA.
79 POTIGA causes skin, scleral, nail, and mucous membrane discoloration and it is not clear
80 whether this discoloration is related to retinal abnormalities [see *Warnings and Precautions*
81 (5.3)]. Approximately 15% of patients with retinal pigmentary abnormalities had no such
82 discoloration.

83 Funduscopy abnormalities have most commonly been described as perivascular
84 pigmentation (bone spicule pattern) in the retinal periphery and/or as areas of focal retinal
85 pigment epithelium clumping. Although some of the patients with retinal abnormalities have
86 been found to have abnormal visual acuity, it is not possible to assess whether POTIGA caused
87 their decreased visual acuity, as baseline assessments are not available for these patients. Two
88 patients with retinal abnormalities have had more extensive diagnostic retinal evaluations. The
89 results of these evaluations were consistent with a retinal dystrophy, including abnormalities in
90 the electroretinogram and electrooculogram of both patients, with abnormal fluorescein
91 angiography and diminished sensitivity on visual field testing in one patient.

92 The rate of progression of retinal abnormalities and the reversibility after drug
93 discontinuation are unknown.

94 Because of the observed ophthalmologic adverse reactions, POTIGA should only be used
95 in patients who have responded inadequately to several alternative treatments and for whom the
96 benefits outweigh the risk of retinal abnormalities and potential vision loss. Patients who fail to
97 show substantial clinical benefit after adequate titration should be discontinued from POTIGA.

98 Patients should have baseline ophthalmologic testing by an ophthalmic professional and
99 follow-up testing every 6 months. The best method of detection of these abnormalities and the
100 optimal frequency of periodic ophthalmologic monitoring are unknown. Patients who cannot be
101 monitored should usually not be treated with POTIGA. The ophthalmologic monitoring program
102 should include visual acuity testing and dilated fundus photography. Additional testing may
103 include fluorescein angiograms (FA), ocular coherence tomography (OCT), perimetry, and
104 electroretinograms (ERG). If retinal pigmentary abnormalities or vision changes are detected,
105 POTIGA should be discontinued unless no other suitable treatment options are available and the
106 benefits of treatment outweigh the potential risk of vision loss.

107 **5.2 Urinary Retention**

108 POTIGA caused urinary retention in clinical trials. Urinary retention was generally
109 reported within the first 6 months of treatment, but was also observed later. Urinary retention
110 was reported as an adverse event in 29 of 1,365 (approximately 2%) patients treated with
111 POTIGA in the open-label and placebo-controlled epilepsy database [see *Clinical Studies (14)*].
112 Of these 29 patients, 5 (17%) required catheterization, with post-voiding residuals of up to
113 1,500 mL. POTIGA was discontinued in 4 patients who required catheterization. Following
114 discontinuation, these 4 patients were able to void spontaneously; however, 1 of the 4 patients

115 continued intermittent self-catheterization. A fifth patient continued treatment with POTIGA and
116 was able to void spontaneously after catheter removal. Hydronephrosis occurred in 2 patients,
117 one of whom had associated renal function impairment that resolved upon discontinuation of
118 POTIGA. Hydronephrosis was not reported in placebo patients.

119 In the placebo-controlled epilepsy trials, “urinary retention,” “urinary hesitation,” and
120 “dysuria” were reported in 0.9%, 2.2%, and 2.3% of patients on POTIGA, respectively, and in
121 0.5%, 0.9%, and 0.7% of patients on placebo, respectively.

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

129 **5.3 Skin Discoloration**

130 POTIGA can cause skin discoloration. The skin discoloration is generally described as
131 blue, but has also been described as grey-blue or brown. It is predominantly on or around the lips
132 or in the nail beds of the fingers or toes, but more widespread involvement of the face and legs
133 has also been reported. Discoloration of the palate, sclera, and conjunctiva has also been
134 reported.

135 Approximately 10% of patients in long-term clinical trials developed skin discoloration,
136 generally after 2 or more years of treatment and at higher doses (900 mg or greater) of POTIGA.
137 Among patients in whom the status of both skin, nail, lip, or mucous membrane discoloration
138 and retinal pigmentary abnormalities are reported, approximately a quarter of those with skin,
139 nail, lip, or mucous membrane discoloration had concurrent retinal pigmentary abnormalities
140 [see *Warnings and Precautions (5.1)*].

141 Information on the consequences, reversibility, time to onset, and pathophysiology of the
142 skin abnormalities remains incomplete. The possibility of more extensive systemic involvement
143 has not been excluded. If a patient develops skin discoloration, serious consideration should be
144 given to changing to an alternate medication.

145 **5.4 Neuro-Psychiatric Symptoms**

146 Confusional state, psychotic symptoms, and hallucinations were reported more frequently
147 as adverse reactions in patients treated with POTIGA than in those treated with placebo in
148 placebo-controlled epilepsy trials (see Table 2). Discontinuations resulting from these reactions
149 were more common in the drug-treated group (see Table 2). These effects were dose-related and
150 generally appeared within the first 8 weeks of treatment. Half of the patients in the controlled
151 trials who discontinued POTIGA due to hallucinations or psychosis required hospitalization.
152 Approximately two-thirds of patients with psychosis in controlled trials had no prior psychiatric
153 history. The psychiatric symptoms in the vast majority of patients in both controlled and open-

154 label trials resolved within 7 days of discontinuation of POTIGA. Rapid titration at greater than
 155 the recommended doses appeared to increase the risk of psychosis and hallucinations.

156

157 **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

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

159

160 **5.5 Dizziness and Somnolence**

161 POTIGA causes dose-related increases in dizziness and somnolence [*see Adverse*
 162 *Reactions (6.1)*]. In placebo-controlled trials in patients with epilepsy, dizziness was reported in
 163 23% of patients treated with POTIGA and 9% of patients treated with placebo. Somnolence was
 164 reported in 22% of patients treated with POTIGA and 12% of patients treated with placebo. In
 165 these trials 6% of patients on POTIGA and 1.2% on placebo discontinued treatment because of
 166 dizziness; 3% of patients on POTIGA and <1.0% on placebo discontinued because of
 167 somnolence.

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

171 **5.6 QT Interval Effect**

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

178 **5.7 Suicidal Behavior and Ideation**

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

183 Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive-therapy)
 184 of 11 different AEDs showed that patients randomized to one of the AEDs had approximately
 185 twice the risk (adjusted relative risk 1.8, 95% confidence interval [CI]: 1.2, 2.7) of suicidal
 186 thinking or behavior compared to patients randomized to placebo. In these trials, which had a

187 median treatment duration of 12 weeks, the estimated incidence of suicidal behavior or ideation
 188 among 27,863 AED-treated patients was 0.43% compared to 0.24% among 16,029 placebo-
 189 treated patients, representing an increase of approximately 1 case of suicidal thinking or behavior
 190 for every 530 patients treated. There were 4 suicides in drug-treated patients in the trials and
 191 none in placebo-treated patients, but the number is too small to allow any conclusion about drug
 192 effect on suicide.

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

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

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

202

203 **Table 3. Risk of Suicidal Thoughts or Behaviors by Indication for Antiepileptic Drugs in**
 204 **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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206 The relative risk for suicidal thoughts or behavior was higher in clinical trials in patients
 207 with epilepsy than in clinical trials in patients with psychiatric or other conditions, but the
 208 absolute risk differences were similar for epilepsy and psychiatric indications.

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

215 Patients, their caregivers, and families should be informed that AEDs increase the risk of
 216 suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or

217 worsening of the signs and symptoms of depression; any unusual changes in mood or behavior;
218 or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of
219 concern should be reported immediately to healthcare providers.

220 **5.8 Withdrawal Seizures**

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

225 **6 ADVERSE REACTIONS**

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

- 228 • Retinal abnormalities and potential vision loss [*see Warnings and Precautions (5.1)*]
- 229 • Urinary retention [*see Warnings and Precautions (5.2)*]
- 230 • Skin discoloration [*see Warnings and Precautions (5.3)*]
- 231 • Neuro-psychiatric symptoms [*see Warnings and Precautions (5.4)*]
- 232 • Dizziness and somnolence [*see Warnings and Precautions (5.5)*]
- 233 • QT interval effect [*see Warnings and Precautions (5.6)*]
- 234 • Suicidal behavior and ideation [*see Warnings and Precautions (5.7)*]
- 235 • Withdrawal seizures [*see Warnings and Precautions (5.8)*]

236 **6.1 Clinical Trials Experience**

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

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

245 Adverse Reactions Leading to Discontinuation in All Controlled Clinical Studies:

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

251 Common Adverse Reactions in All Controlled Clinical Studies: Overall, the most
252 frequently reported adverse reactions in patients receiving POTIGA ($\geq 4\%$ and occurring
253 approximately twice the placebo rate) were dizziness (23%), somnolence (22%), fatigue (15%),
254 confusional state (9%), vertigo (8%), tremor (8%), abnormal coordination (7%), diplopia (7%),
255 disturbance in attention (6%), memory impairment (6%), asthenia (5%), blurred vision (5%), gait

256 disturbance (4%), aphasia (4%), dysarthria (4%), and balance disorder (4%). In most cases the
 257 reactions were of mild or moderate intensity.

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259 **Table 4. Adverse Reaction Incidence in Placebo-Controlled Adjunctive Trials in Adult**
 260 **Patients With Partial Onset Seizures (Adverse reactions in at least 2% of patients treated**
 261 **with POTIGA in any treatment group and numerically more frequent than in the placebo**
 262 **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
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, myoclonus, peripheral edema, hypokinesia, dry mouth, dysphagia, hyperhidrosis, urinary retention, malaise, and increased liver enzymes.

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

POTIGA was associated with dose-related weight gain, with mean weight increasing by 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 per day groups, respectively.

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

Following is a list of adverse reactions reported by patients treated with POTIGA during all

277 clinical trials: rash, nystagmus, dyspnea, leukopenia, muscle spasms, alopecia, nephrolithiasis,
278 syncope, neutropenia, thrombocytopenia, euphoric mood, renal colic, coma, encephalopathy.

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

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

284 **7 DRUG INTERACTIONS**

285 **7.1 Antiepileptic Drugs**

286 The potentially significant interactions between POTIGA and concomitant AEDs are
287 summarized in Table 5.

288

289 **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

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

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

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

294 [See *Clinical Pharmacology (12.3)*]

295

296 **7.2 Digoxin**

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

302 7.3 Alcohol

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

306 7.4 Laboratory Tests

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

309 8 USE IN SPECIFIC POPULATIONS**310 8.1 Pregnancy**

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

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

319 Treatment of pregnant rats with ezogabine (oral doses of up to 46 mg/kg/day) throughout
320 organogenesis increased the incidences of fetal skeletal variations. The no-effect dose for
321 embryo-fetal toxicity in rats (21 mg/kg/day) was associated with maternal plasma exposures
322 (AUC) to ezogabine and NAMR less than those in humans at the MRHD. Treatment of pregnant
323 rabbits with ezogabine (oral doses of up to 60 mg/kg/day) throughout organogenesis resulted in
324 decreased fetal body weights and increased incidences of fetal skeletal variations. The no-effect
325 dose for embryo-fetal toxicity in rabbits (12 mg/kg/day) was associated with maternal plasma
326 exposures to ezogabine and NAMR less than those in humans at the MRHD.

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

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

337 8.2 Labor and Delivery

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

339 8.3 Nursing Mothers

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

345 8.4 Pediatric Use

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

348 In juvenile animal studies, increased sensitivity to acute neurotoxicity and urinary bladder
349 toxicity was observed in young rats compared to adults. In studies in which rats were dosed
350 starting on postnatal day 7, ezogabine-related mortality, clinical signs of neurotoxicity, and renal
351 and urinary tract toxicities were observed at doses ≥ 2 mg/kg/day. The no-effect level was
352 associated with plasma ezogabine exposures (AUC) less than those expected in human adults at
353 the MRHD of 1,200 mg per day. In studies in which dosing began on postnatal day 28, acute
354 central nervous system effects, but no apparent renal or urinary tract effects, were observed at
355 doses of up to 30 mg/kg/day. These doses were associated with plasma ezogabine exposures less
356 than those achieved clinically at the MRHD.

357 8.5 Geriatric Use

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

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

364 8.6 Patients With Renal Impairment

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

368 8.7 Patients With Hepatic Impairment

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

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

373 9 DRUG ABUSE AND DEPENDENCE**374 9.1 Controlled Substance**

375 POTIGA is a Schedule V controlled substance.

376 9.2 Abuse

377 A human abuse potential study was conducted in recreational sedative-hypnotic abusers
378 (n = 36) in which single oral doses of ezogabine (300 mg [n = 33], 600 mg [n = 34], 900 mg
379 [n = 6]), the sedative-hypnotic alprazolam (1.5 mg and 3.0 mg), and placebo were administered.
380 Euphoria-type subjective responses to the 300-mg and 600-mg doses of ezogabine were
381 statistically different from placebo but statistically indistinguishable from those produced by
382 either dose of alprazolam. Adverse events reported following administration of single oral doses
383 of 300 mg, 600 mg, and 900 mg ezogabine given without titration included euphoric mood (18%,
384 21%, and 33%, respectively; 8% from placebo), hallucination (0%, 0%, and 17%, respectively;
385 0% from placebo) and somnolence (18%, 15%, and 67%, respectively; 15% from placebo).

386 In Phase 1 clinical studies, healthy individuals who received oral ezogabine (200 mg to
387 1,650 mg) reported euphoria (8.5%), feeling drunk (5.5%), hallucination (5.1%), disorientation
388 (1.7%), and feeling abnormal (1.5%).

389 In the 3 randomized, double-blind, placebo-controlled Phase 2 and 3 clinical studies,
390 patients with partial seizures who received oral ezogabine (300 mg to 1,200 mg) reported
391 euphoric mood (0.5%) and feeling drunk (0.9%), while those who received placebo did not
392 report either adverse event (0%).

393 **9.3 Dependence**

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

398 **10 OVERDOSAGE**

399 **10.1 Signs, Symptoms, and Laboratory Findings**

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

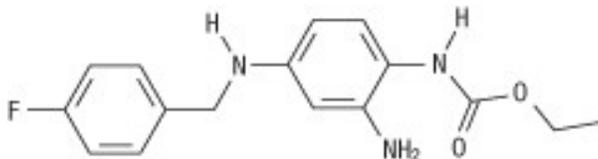
404 In an abuse potential study, cardiac arrhythmia (asystole or ventricular tachycardia)
405 occurred in 2 volunteers within 3 hours of receiving a single 900-mg dose of POTIGA. The
406 arrhythmias spontaneously resolved and both volunteers recovered without sequelae.

407 **10.2 Management of Overdose**

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

413 11 DESCRIPTION

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



416
417 The empirical formula is $C_{16}H_{18}FN_3O_2$, representing a molecular weight of 303.3.
418 Ezogabine is a white to slightly colored, odorless, tasteless, crystalline powder. At room
419 temperature, ezogabine is practically insoluble in aqueous media at pH values above 4, while the
420 solubility is higher in polar organic solvents. At gastric pH, ezogabine is sparingly soluble in
421 water (about 16 g/L). The pKa is approximately 3.7 (basic).

422 POTIGA is supplied for oral administration as 50-mg, 200-mg, 300-mg, and 400-mg
423 film-coated immediate-release tablets. Each tablet contains the labeled amount of ezogabine and
424 the following inactive ingredients: carmine (50-mg and 400-mg tablets), croscarmellose sodium,
425 FD&C Blue No. 2 (50-mg, 300-mg, and 400-mg tablets), hypromellose, iron oxide yellow
426 (200-mg and 300-mg tablets), lecithin, magnesium stearate, microcrystalline cellulose, polyvinyl
427 alcohol, talc, titanium dioxide, and xanthan gum.

428 12 CLINICAL PHARMACOLOGY**429 12.1 Mechanism of Action**

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

436 12.2 Pharmacodynamics

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

445 Patients who are prescribed POTIGA with medicines known to increase QT interval or
446 who have known prolonged QT interval, congestive heart failure, ventricular hypertrophy,

447 hypokalemia, or hypomagnesemia should be observed closely [see Warnings and Precautions
448 (5.4)].

449 **12.3 Pharmacokinetics**

450 The pharmacokinetic profile is approximately linear in daily doses between 600 mg and
451 1,200 mg in patients with epilepsy, with no unexpected accumulation following repeated
452 administration. The pharmacokinetics of ezogabine are similar in healthy volunteers and patients
453 with epilepsy.

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

460 POTIGA can be taken with or without food.

461 **Distribution:** Data from *in vitro* studies indicate that ezogabine and NAMR are
462 approximately 80% and 45% bound to plasma protein, respectively. Clinically significant
463 interactions with other drugs through displacement from proteins are not anticipated. The steady-
464 state volume of distribution of ezogabine is 2 to 3 L/kg following intravenous dosing, suggesting
465 that ezogabine is well distributed in the body.

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

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

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

486 Ezogabine and its N-acetyl metabolite have similar elimination half-lives ($t_{1/2}$) of 7 to 11
487 hours. The clearance of ezogabine following intravenous dosing was approximately 0.4 to
488 0.6 L/hr/kg. Ezogabine is actively secreted into the urine.

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

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

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

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

511 *Renal Impairment:* The pharmacokinetics of ezogabine were studied following a
512 single 100-mg dose of POTIGA in subjects with normal ($CrCL >80$ ml/min), mild ($CrCL \geq 50$ to
513 <80 mL/min), moderate ($CrCL \geq 30$ to <50 mL/min), or severe renal impairment ($CrCL <30$
514 mL/min) ($n = 6$ in each cohort) and in subjects with ESRD requiring hemodialysis ($n = 6$). The
515 ezogabine AUC was increased by approximately 30% in patients with mild renal impairment and
516 doubled in patients with moderate impairment to ESRD ($CrCL <50$ mL/min) relative to healthy
517 subjects. Similar increases in NAMR exposure were observed in the various degrees of renal
518 impairment. The effect of hemodialysis on ezogabine clearance has not been established. Dosage
519 reduction is recommended for patients with creatinine clearance <50 mL/min and for patients
520 with ESRD receiving dialysis [*see Dosage and Administration (2), Use in Specific Populations*
521 *(8.6)*].

522 *Hepatic Impairment:* The pharmacokinetics of ezogabine were studied following a
523 single 100-mg dose of POTIGA in subjects with normal, mild (Child-Pugh score 5 to 6),
524 moderate (Child-Pugh score 7 to 9), or severe hepatic (Child-Pugh score >9) impairment ($n = 6$

525 in each cohort). Relative to healthy subjects, ezogabine AUC was not affected by mild hepatic
 526 impairment, but was increased by approximately 50% in subjects with moderate hepatic
 527 impairment and doubled in subjects with severe hepatic impairment. There was an increase of
 528 approximately 30% in exposure to NAMR in patients with moderate to severe impairment.
 529 Dosage reduction is recommended for patients with moderate and severe hepatic impairment
 530 [see *Dosage and Administration (2), Use in Specific Populations (8.7)*].

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

538 Ezogabine is neither a substrate nor an inhibitor of P-glycoprotein, an efflux transporter.
 539 NAMR is a P-glycoprotein inhibitor. Data from an *in vitro* study showed that NAMR inhibited
 540 P-glycoprotein-mediated transport of digoxin in a concentration-dependent manner, indicating
 541 that NAMR may inhibit renal clearance of digoxin. Administration of POTIGA at therapeutic
 542 doses may increase digoxin serum concentrations [see *Drug Interactions (7.2)*].

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

545

546 **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

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

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

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

551 ^d Zonisamide, valproic acid, clonazepam, gabapentin, levetiracetam, oxcarbazepine,
552 phenobarbital, pregabalin, topiramate, clobazam, and lamotrigine, based on a population
553 pharmacokinetic analysis using pooled data from Phase 3 clinical trials.
554

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

559 In a second study examining the potential interaction of repeated ezogabine dosing
560 (250 mg 3 times daily for 14 days) and the combination oral contraceptive norethindrone/ethinyl
561 estradiol (1 mg/0.035 mg) tablets in 25 healthy females, no significant alteration in the
562 pharmacokinetics of either drug was observed.

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

566 **13 NONCLINICAL TOXICOLOGY**

567 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

585 **14 CLINICAL STUDIES**

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

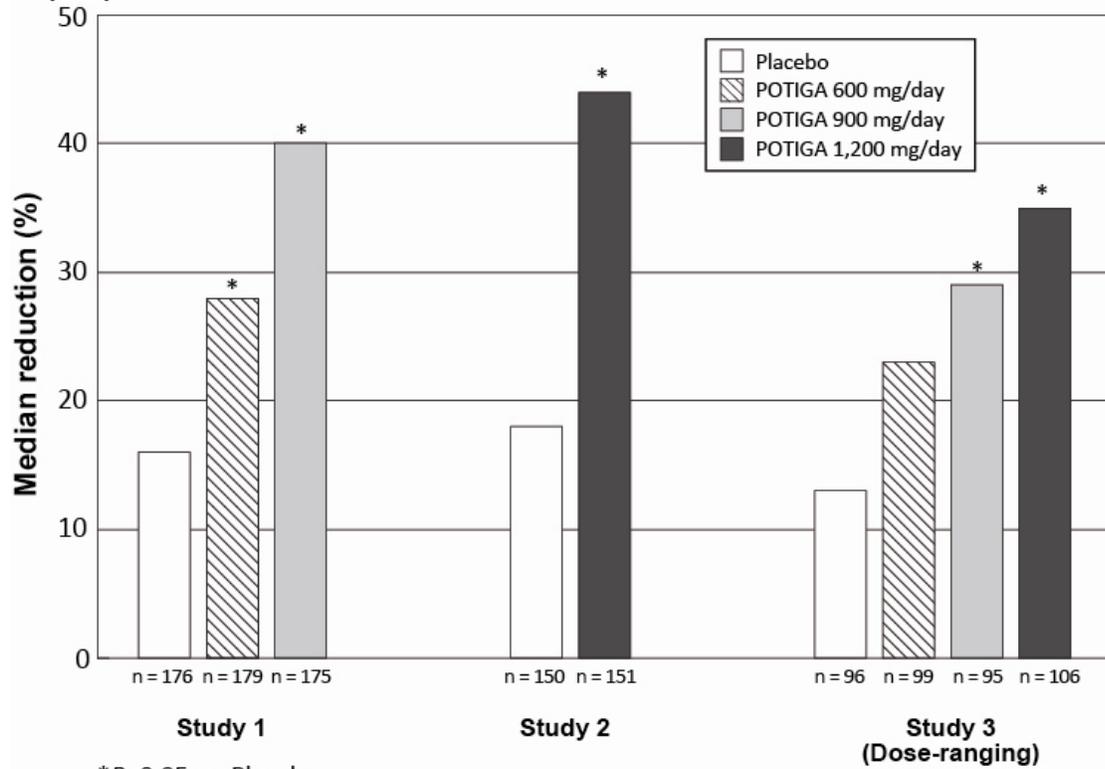
590 Patients enrolled in the studies had partial onset seizures with or without secondary
591 generalization and were not adequately controlled with 1 to 3 concomitant AEDs, with or
592 without concomitant vagus nerve stimulation. More than 75% of patients were taking 2 or more
593 concomitant AEDs. During an 8-week baseline period, patients experienced at least 4 partial
594 onset seizures per 28 days on average with no seizure-free period exceeding 3 to 4 weeks.
595 Patients had a mean duration of epilepsy of 22 years. Across the 3 studies, the median baseline
596 seizure frequency ranged from 8 to 12 seizures per month. The criteria for statistical significance
597 was $P < 0.05$.

598 Patients were randomized to the total daily maintenance dosages of 600 mg per day,
599 900 mg per day, or 1,200 mg per day, each administered in 3 equally divided doses. During the
600 titration phase of all 3 studies, treatment was initiated at 300 mg per day (100 mg 3 times per
601 day) and increased in weekly increments of 150 mg per day to the target maintenance dosage.

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

606

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



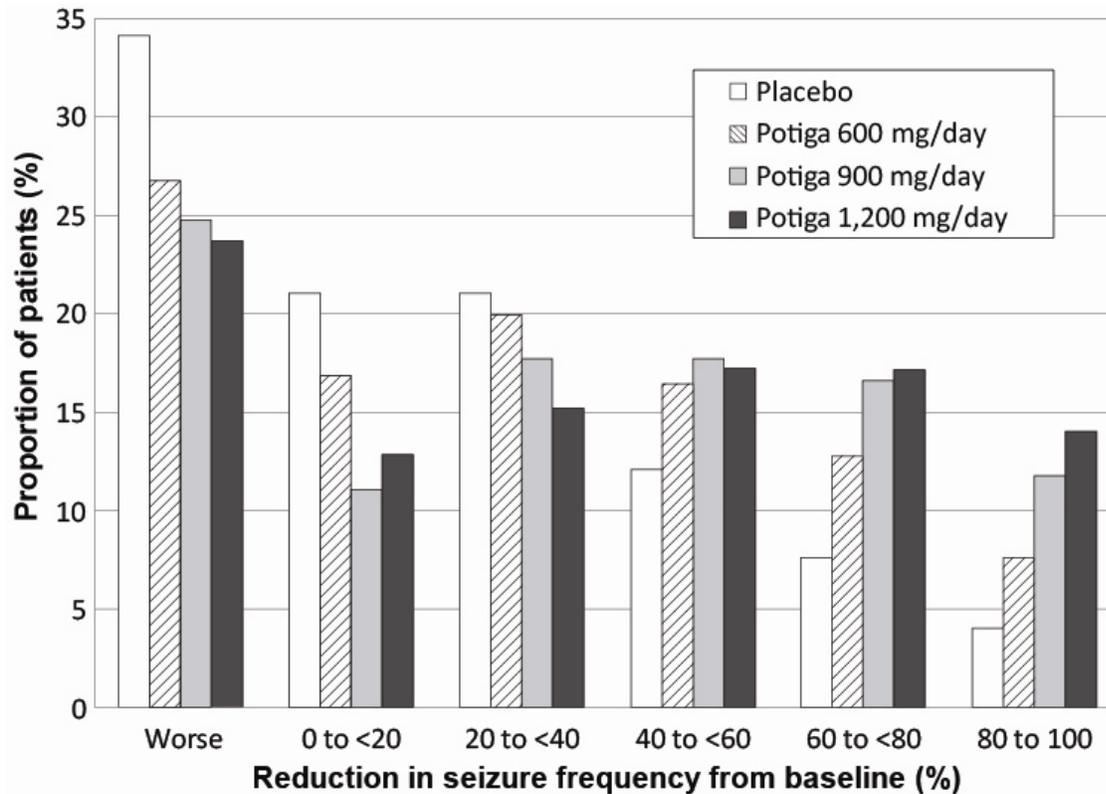
*P<0.05 vs. Placebo

609
610

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

615

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



618

619 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

622 **50-mg Tablets:** purple, round, film-coated tablets debossed with “RTG 50” on one side in
 623 bottles of 90 tablets with desiccant (NDC 0173-0810-59).

624 **200-mg Tablets:** yellow, oblong, film-coated tablets debossed with “RTG-200” on one side in
 625 bottles of 90 tablets with desiccant (NDC 0173-0812-59).

626 **300-mg Tablets:** green, oblong, film-coated tablets debossed with “RTG-300” on one side in
 627 bottles of 90 tablets with desiccant (NDC 0173-0813-59).

628 **400-mg Tablets:** purple, oblong, film-coated tablets debossed with “RTG-400” on one side in
 629 bottles of 90 tablets with desiccant (NDC 0173-0814-59).

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

632 **17 PATIENT COUNSELING INFORMATION**

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

634 **17.1 Retinal Abnormalities and Potential Vision Loss**

635 Inform patients of the risk of retinal abnormalities and possible risk of vision loss, which
636 may be permanent [see *Warnings and Precautions 5.1*]. All patients taking POTIGA should
637 participate in baseline and periodic ophthalmologic monitoring of vision by an ophthalmic
638 professional. Inform patients that if they suspect any vision changes, they should notify their
639 physician immediately.

640 **17.2 Urinary Retention**

641 Patients should be informed that POTIGA can cause urinary retention (including urinary
642 hesitation and dysuria). If patients experience any symptoms of urinary retention, inability to
643 urinate, and/or pain with urination, they should be instructed to seek immediate medical
644 assistance [see *Warnings and Precautions (5.2)*]. For patients who cannot reliably report
645 symptoms of urinary retention (for example, patients with cognitive impairment), urologic
646 consultation may be helpful.

647 **17.3 Skin Discoloration**

648 Inform patients that POTIGA can cause discoloration of nails, lips, skin, palate, and parts
649 of the eye and that it is not known if the discoloration is reversible upon drug discontinuation
650 [see *Warnings and Precautions 5.3*]. Most skin discoloration has been reported after at least 2
651 years of treatment with POTIGA, but may happen earlier. Inform patients that the possibility of
652 more extensive systemic involvement has not been excluded. Instruct patients to notify their
653 physician if they develop skin discoloration.

654 **17.4 Psychiatric Symptoms**

655 Patients should be informed that POTIGA can cause psychiatric symptoms such as
656 confusional state, disorientation, hallucinations, and other symptoms of psychosis. Patients and
657 their caregivers should be instructed to notify their physicians if they experience psychotic
658 symptoms [see *Warnings and Precautions (5.4)*].

659 **17.5 Central Nervous System Effects**

660 Patients should be informed that POTIGA may cause dizziness, somnolence, memory
661 impairment, abnormal coordination/balance, disturbance in attention, and ophthalmological
662 effects such as diplopia or blurred vision. Patients taking POTIGA should be advised not to
663 drive, operate complex machinery, or engage in other hazardous activities until they have
664 become accustomed to any such effects associated with POTIGA [see *Warnings and Precautions*
665 *(5.5)*].

666 **17.6 Suicidal Thinking and Behavior**

667 Patients, their caregivers, and families should be informed that AEDs, including
668 POTIGA, may increase the risk of suicidal thoughts and behavior and should be advised of the
669 need to be alert for the emergence or worsening of symptoms of depression, any unusual changes
670 in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-
671 harm. Behaviors of concern should be reported immediately to healthcare providers [see
672 *Warnings and Precautions (5.7)*].

673 **17.7 Pregnancy**

674 Patients should be advised to notify their physicians if they become pregnant or intend to
675 become pregnant during therapy. Patients should be advised to notify their physicians if they
676 intend to breastfeed or are breastfeeding an infant.

677 Patients should be encouraged to enroll in the NAAED Pregnancy Registry if they
678 become pregnant. This registry collects information about the safety of AEDs during pregnancy.
679 To enroll, patients can call the toll-free number 1-888-233-2334 [*see Use in Specific Populations*
680 (8.1)].

681
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693 **MEDICATION GUIDE**
694 **POTIGA™ (po-TEE-ga) Tablets, CV**
695 **(ezogabine)**

696
697 Read this Medication Guide before you start taking POTIGA and each time you get a
698 refill. There may be new information. This Medication Guide does not take the place
699 of talking to your healthcare provider about your medical condition or treatment. If
700 you have questions about POTIGA, ask your healthcare provider or pharmacist.

701
702 **What is the most important information I should know about POTIGA?**

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

706 **1. POTIGA can cause changes to your retina, which is located in the back**
707 **of your eye and is needed for vision. These types of changes can cause**
708 **vision loss.**

- 709 • If a decrease in your vision happens, it is not known if it will get better.

- 710 • You and your healthcare provider should decide if the benefit of taking
711 POTIGA is more important than the possible risk of vision loss.
- 712 • You should have a complete eye exam if you are currently taking POTIGA or
713 before starting treatment, and then every 6 months while taking POTIGA.
- 714 • Tell your healthcare provider right away if you notice any changes in your
715 vision.
- 716 **2. POTIGA can make it hard for you to urinate** (empty your bladder) and may
717 cause you to be unable to urinate. Call your healthcare provider right away if
718 you:
- 719 • are unable to start urinating
- 720 • have trouble emptying your bladder
- 721 • have a weak urine stream
- 722 • have pain with urination
- 723 **3. POTIGA can cause changes in the color of your skin, nails, lips, roof of**
724 **your mouth, and whites of your eyes or insides of your eyelids.**
- 725 • The changes in color may be blue, grey-blue, or brown.
- 726 • Most changes in color have happened in people who have taken POTIGA for
727 at least 2 years, but may happen earlier.
- 728 • It is not known if the changes in color go away after stopping POTIGA.
- 729 • Tell your healthcare provider if you notice any changes in color to your body.
- 730 **4. POTIGA can cause mental (psychiatric) problems, including:**
- 731 • confusion
- 732 • new or worse aggressive behavior, hostility, anger, or irritability
- 733 • new or worse psychosis (hearing or seeing things that are not real)
- 734 • being suspicious or distrustful (believing things that are not true)
- 735 • other unusual or extreme changes in behavior or mood
- 736 Tell your healthcare provider right away if you have any new or worsening
737 mental problems while using POTIGA.
- 738 **5. Like other antiepileptic drugs, POTIGA may cause suicidal thoughts or**
739 **actions in a very small number of people, about 1 in 500.**

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

- 742 • thoughts about suicide or dying
- 743 • attempt to commit suicide
- 744 • new or worse depression
- 745 • new or worse anxiety
- 746 • feeling agitated or restless
- 747 • panic attacks
- 748 • trouble sleeping (insomnia)
- 749 • new or worse irritability
- 750 • acting aggressive, being angry, or violent
- 751 • acting on dangerous impulses
- 752 • an extreme increase in activity and talking (mania)
- 753 • other unusual changes in behavior or mood

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

757
758 **How can I watch for early symptoms of suicidal thoughts and actions?**

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

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

764
765 **What is POTIGA?**

766 POTIGA is a prescription medicine that is used with other medicines to treat partial-
767 onset seizures in adults with epilepsy when several other medicines have not
768 worked well. POTIGA is used when the benefit of taking it is more important than
769 the possible risk of vision loss.

770 POTIGA is a controlled substance (CV) because it can be abused or lead to drug
771 dependence. Keep your POTIGA in a safe place to protect it from theft. Never give

772 your POTIGA to anyone else because it may harm them. Selling or giving away this
773 medicine is against the law.

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

775

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

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

- 778 • have trouble urinating
- 779 • have an enlarged prostate
- 780 • have or have had depression, mood problems, or suicidal thoughts or behavior
- 781 • have heart problems, including a condition called long QT Syndrome, or have
782 low potassium or magnesium in your blood
- 783 • have liver problems
- 784 • have kidney problems
- 785 • drink alcohol
- 786 • have any other medical conditions
- 787 • are pregnant or plan to become pregnant. It is not known if POTIGA will harm
788 your unborn baby.
 - 789 • If you become pregnant while taking POTIGA, talk to your healthcare
790 provider about registering with the North American Antiepileptic Drug
791 Pregnancy Registry. The purpose of this registry is to collect information
792 about the safety of medicines used to treat seizures during pregnancy. You
793 can enroll in this registry by calling 1-888-233-2334.
- 794 • are breastfeeding or plan to breastfeed. It is not known if POTIGA passes into
795 your breast milk. Talk to your healthcare provider about the best way to feed
796 your baby if you take POTIGA. You and your healthcare provider should decide if
797 you will take POTIGA or breastfeed. You should not do both.

798 **Tell your healthcare provider about all the medicines you take**, including
799 prescription and over-the-counter medicines, vitamins, and herbal supplements.

800 Taking POTIGA with certain other medicines can affect each other, causing side
801 effects.

802 **Especially tell your healthcare provider if you take:**

- 803 • digoxin (LANOXIN®)
- 804 • phenytoin (DILANTIN®, PHENYTEK®)

- 805 • carbamazepine (CARBATROL[®], TEGRETOL[®], TEGRETOL[®]-XR, EQUETRO[®],
806 EPITOL[®])

807 Know the medicines you take. Keep a list of them to show your healthcare provider
808 and pharmacist when you get a new medicine.

809

810 **How should I take POTIGA?**

- 811 • Take POTIGA exactly as your healthcare provider tells you to take it. Your
812 healthcare provider will tell you how much POTIGA to take and when to take it.
- 813 • Your healthcare provider may change your dose of POTIGA. Do not change your
814 dose without talking to your healthcare provider.
- 815 • POTIGA can be taken with or without food.
- 816 • Swallow POTIGA tablets whole. Do not break, crush, dissolve, or chew POTIGA
817 tablets before swallowing.
- 818 • If you take too much POTIGA, call your local Poison Control Center or go to the
819 nearest hospital emergency room right away.

820

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

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

825

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

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

- 828 • See "What is the most important information I should know about POTIGA?"
- 829 • **Dizziness and sleepiness.** These symptoms can increase when your dose of
830 POTIGA is increased. See "What should I avoid while taking POTIGA?"
- 831 • **Changes in your heart rhythm and the electrical activity of your heart.**
832 Your healthcare provider should monitor your heart during treatment if you have
833 a certain type of heart disease or take certain medications.
- 834 • Drinking alcohol during treatment with POTIGA may increase the side effects
835 that you get with POTIGA.

836 The most common side effects of POTIGA include:

- 837 • dizziness

- 838 • somnolence
- 839 • sleepiness
- 840 • tiredness
- 841 • confusion
- 842 • spinning sensation (vertigo)
- 843 • tremor
- 844 • problems with balance and muscle coordination, including trouble with walking
- 845 and moving
- 846 • blurred or double vision
- 847 • trouble concentrating
- 848 • memory problems
- 849 • weakness

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

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

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

856

857 **How should I store POTIGA?**

- 858 • Store POTIGA at room temperature between 68°F and 77°F (20°C and 25°C).
- 859 • **Keep POTIGA and all medicines out of the reach of children.**

860

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

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

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

870 For more information, go to www.potiga.com or call 1-877-3POTIGA (1-877-376-
871 8442).

872

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

874 **Active ingredient:** ezogabine

875 **Inactive ingredients in all strengths:** croscarmellose sodium, hypromellose,
876 lecithin, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, talc,
877 titanium dioxide, and xanthan gum

878 50-mg and 400-mg tablets also contain: carmine

879 50-mg, 300-mg, and 400-mg tablets also contain: FD&C Blue No 2

880 200-mg and 300-mg tablets also contain: iron oxide yellow

881

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885 trademarks of GlaxoSmithKline. The makers of these brands are not affiliated with
886 and do not endorse GlaxoSmithKline or its products.

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

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898 September 2013

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