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 ≥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:

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

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

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

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

POTIGA Tablets should be swallowed whole.

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

Table 1. Dosing Recommendations

Specific Population	Initial Dose	Titration	Maximum Dose
General Dosing			
General population (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			
Geriatrics (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)
Renal impairment (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)
Hepatic impairment (patients with Child-Pugh 7-9)	50 mg 3 times daily (150 mg per day)		250 mg 3 times daily (750 mg per day)
Hepatic impairment (patients with Child-Pugh >9)	50 mg 3 times daily (150 mg per day)		200 mg 3 times daily (600 mg per day)

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Urinary Retention

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

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

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

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

5.2 Neuro-Psychiatric Symptoms

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

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

	Number (%) With Adverse Reaction		Number (%) Discontinuing	
Adverse Reaction	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

[a] Hallucinations includes visual, auditory, and mixed hallucinations.

5.3 Dizziness and Somnolence

POTIGA causes dose-related increases in dizziness and somnolence *[see Adverse Reactions (6.1)]*. In placebo-controlled trials in patients with epilepsy, dizziness was reported in 23% of patients treated with POTIGA and 9% of patients treated with placebo. Somnolence was

reported in 22% of patients treated with POTIGA and 12% of patients treated with placebo. In these trials 6% of patients on POTIGA and 1.2% on placebo discontinued treatment because of dizziness; 3% of patients on POTIGA and <1.0% on placebo discontinued because of somnolence.

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

5.4 QT Interval Effect

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

5.5 Suicidal Behavior and Ideation

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

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

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

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

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

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

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.

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.

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.

5.6 Withdrawal Seizures

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.

6 ADVERSE REACTIONS

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

- 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)]*
- QT interval effect *[see Warnings and Precautions (5.4)]*
- Suicidal behavior and ideation *[see Warnings and Precautions (5.5)]*

- Withdrawal seizures *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

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

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

Adverse Reactions Leading to Discontinuation in All Controlled Clinical Studies: In the 3 randomized, double-blind, placebo-controlled studies, 199 of 813 patients (25%) receiving POTIGA and 45 of 427 patients (11%) receiving placebo discontinued treatment because of adverse reactions. The most common adverse reactions leading to withdrawal in patients receiving POTIGA were dizziness (6%), confusional state (4%), fatigue (3%), and somnolence (3%).

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

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

		POTIGA			
	Placebo	600 mg/day	900 mg/day	1,200 mg/day	All
Body System/ Adverse Reaction	(N = 427) %	(N = 281) %	(N = 273) %	(N = 259) %	(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

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

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

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

7 DRUG INTERACTIONS

7.1 Antiepileptic Drugs

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

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]

[a] Based on results of a Phase 2 study.

[b] Inducer for uridine 5'-diphosphate (UDP)-glucuronyltransferases (UGTs).

[c] A decrease in dosage of POTIGA should be considered when carbamazepine or phenytoin is discontinued.

[See Clinical Pharmacology (12.3)]

7.2 Digoxin

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

7.3 Alcohol

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

7.4 Laboratory Tests

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

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

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

Pregnancy Registry: To provide information regarding the effects of *in utero* exposure to POTIGA, physicians are advised to recommend that pregnant patients taking POTIGA enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by

calling the toll-free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website www.aedpregnancyregistry.org.

8.2 Labor and Delivery

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

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

8.5 Geriatric Use

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

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

8.6 Patients With Renal Impairment

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

8.7 Patients With Hepatic Impairment

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

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

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

POTIGA is a Schedule V controlled substance.

9.2 Abuse

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

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

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

9.3 Dependence

There are no adequate data to assess the ability of ezogabine to induce symptoms of withdrawal indicative of physical dependence. However, the ability of ezogabine to produce psychological dependence is suggested by adverse event reports of euphoric mood (18% [6 of 33 subjects] to 33% [2 of 6 subjects]) in sedative-hypnotic abusers in the human abuse potential study and adverse event reports of euphoria (8.5%) in healthy individuals who participated in Phase 1 studies.

10 OVERDOSAGE

10.1 Signs, Symptoms, and Laboratory Findings

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

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

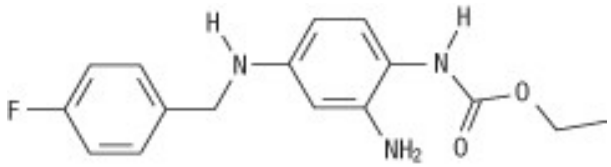
10.2 Management of Overdose

There is no specific antidote for overdose with POTIGA. In the event of overdose, standard medical practice for the management of any overdose should be used. An adequate

airway, oxygenation, and ventilation should be ensured; monitoring of cardiac rhythm and vital sign measurement is recommended. A certified poison control center should be contacted for updated information on the management of overdose with POTIGA.

11 DESCRIPTION

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



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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

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

12.3 Pharmacokinetics

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

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

POTIGA can be taken with or without food.

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

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

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

Elimination: Results of a mass balance study suggest that renal excretion is the major route of elimination for ezogabine and NAMR. About 85% of the dose was recovered in the urine, with the unchanged parent drug and NAMR accounting for 36% and 18% of the administered dose, respectively, and the total N-glucuronides of ezogabine and NAMR accounting for 24% of the administered dose. Approximately 14% of the radioactivity was

recovered in the feces, with unchanged ezogabine accounting for 3% of the total dose. Average total recovery in both urine and feces within 240 hours after dosing is approximately 98%.

Ezogabine and its N-acetyl metabolite have similar elimination half-lives ($t_{½}$) of 7 to 11 hours. The clearance of ezogabine following intravenous dosing was approximately 0.4 to 0.6 L/hr/kg. Ezogabine is actively secreted into the urine.

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

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

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

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

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

Hepatic Impairment: The pharmacokinetics of ezogabine were studied following a single 100-mg dose of POTIGA in subjects with normal, mild (Child-Pugh score 5 to 6),

moderate (Child-Pugh score 7 to 9), or severe hepatic (Child-Pugh score >9) impairment (n = 6 in each cohort). Relative to healthy subjects, ezogabine AUC was not affected by mild hepatic impairment, but was increased by approximately 50% in subjects with moderate hepatic impairment and doubled in subjects with severe hepatic impairment. There was an increase of approximately 30% in exposure to NAMR in patients with moderate to severe impairment. Dosage reduction is recommended for patients with moderate and severe hepatic impairment *[see Dosage and Administration (2), Use in Specific Populations (8.7)]*.

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

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

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

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	None	None

			in AUC, 22% increase in clearance		
Others[d]			None	None	None

[a] Based on results of a Phase 2 study.
[b] Inducer for uridine 5'-diphosphate (UDP)-glucuronyltransferases (UGTs).
[c] A decrease in dose of POTIGA should be considered when carbamazepine or phenytoin is discontinued.
[d] Zonisamide, valproic acid, clonazepam, gabapentin, levetiracetam, oxcarbazepine, phenobarbital, pregabalin, topiramate, clobazam, and lamotrigine, based on a population pharmacokinetic analysis using pooled data from Phase 3 clinical trials.

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

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

Impairment of Fertility: Ezogabine had no effect on fertility, general reproductive performance, or early embryonic development when administered to male and female rats at

doses of up to 46.4 mg/kg/day (associated with a plasma ezogabine exposure [AUC] less than that in humans at the MRHD) prior to and during mating, and continuing in females through gestation day 7.

14 CLINICAL STUDIES

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

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

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

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

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

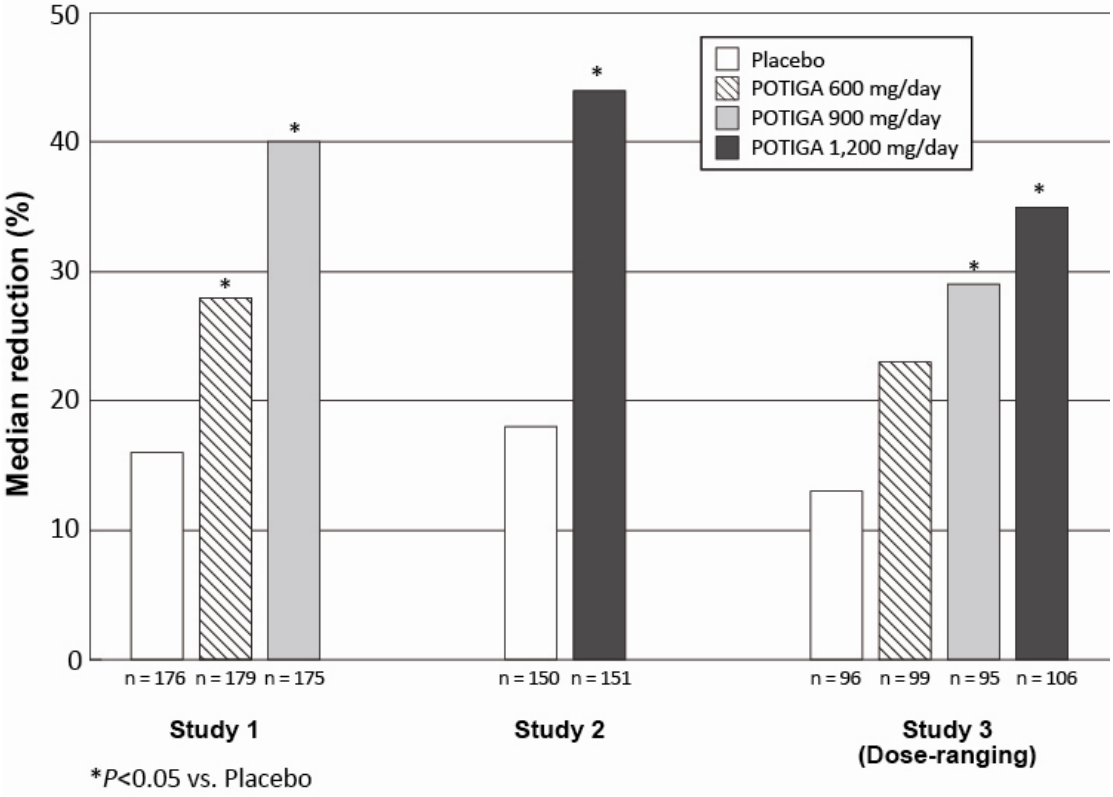
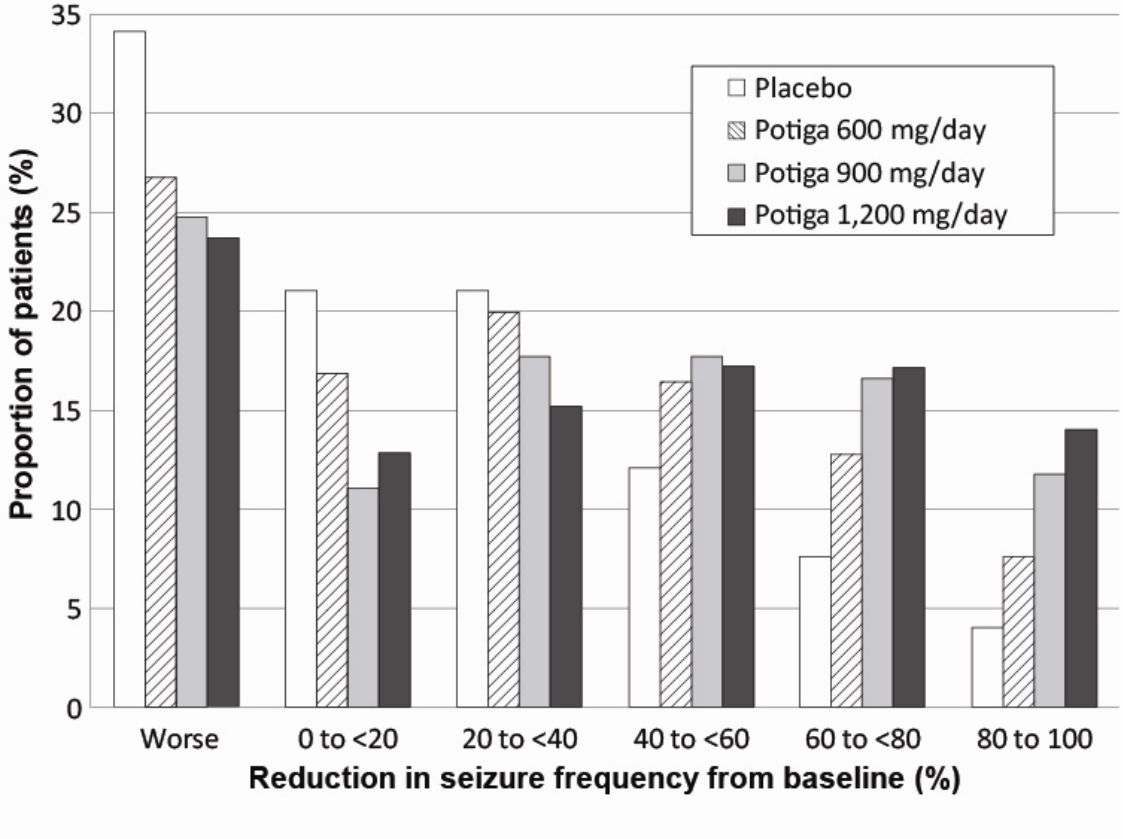


Figure 2 shows changes from baseline in the 28-day total partial seizure frequency by category for patients treated with POTIGA and placebo in an integrated analysis across the 3 clinical trials. Patients in whom the seizure frequency increased are shown at left as "worse." Patients in whom the seizure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

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



16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

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

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

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

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

17.1 Urinary Retention

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

17.2 Psychiatric Symptoms

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

17.3 Central Nervous System Effects

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

17.4 Suicidal Thinking and Behavior

Patients, their caregivers, and families should be informed that AEDs, including POTIGA, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of 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 *[see Warnings and Precautions (5.5)]*.

17.5 Pregnancy

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

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

POTIGA is a trademark of Valeant Pharmaceuticals North America.