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Abbreviated Update: Oral Anticonvulsants
New Drug: ezogabine (Potiga)

Month/Year of Review: May 2012
Current PDL Class: Oral Anticonvulsants
New drugs: ezogabine (Potiga™) **Manufacturer:** GlaxoSmithKline

Current Preferred Agents:			Current Non-Preferred Agents:
Carbamazepine	Lamotrigine	Rufinamide (Banzel)	Felbamate (Felbatol)
Carbamazepine ER (Tegretol XR)	Levetiracetam	Tiagabine (Gabitril)	Pregabalin (Lyrica)
Clonazepam	Methobarbital (Mebaral)	Topiramate	Vigabatrin (Sabril)
Diastat (Brand only)	Methosuximide (Cleontin)	Valproic Acid	
Divalproex	Oxcarbazepine	Zonisamide	
Ethosuximide	Phenobarbital	Gabapentin	
Ethotoin (Peganone)	Phenytoin	Lacosamide (Vimpat)	
Primidone			

Research Questions:

- Is there any new relative evidence from high quality systematic reviews or evidence based guidelines suggesting recommended changes to our current management of the PDL class?
- Is ezogabine more effective than currently available agents?
- Is ezogabine safer than currently available agents?
- Are there unique patients or situations where ezogabine may be more effective or safer than currently available agents?

Conclusions:

- There is moderate quality evidence that ezogabine improves response rate in patients with epilepsy when used as adjunct treatment after previous treatment with AEDs has not provided adequate response.
- There is insufficient evidence to evaluate efficacy of ezogabine in the outcome of freedom from seizures.
- There is insufficient evidence to make comparative conclusions with other adjunctive treatments for epilepsy.
- Updated NICE guidelines recommend carbamazepine or lamotrigine as first line agents for focal seizures (moderate to very low quality evidence) and sodium valproate as first line treatment for tonic-clonic seizures (low to very low quality evidence).
- Based on a recent AHRQ review, there in insufficient to low strength of evidence suggesting that switching from an innovator to a generic, generic to generic, or generic to innovator version of the same medication increases the short-term risk of hospitalization and hospital stay duration and increases the short-term risk of a composite of having an emergency department and hospitalization visit with or without ambulance service utilization.

Recommendations:

- Make ezogabine a second line non-preferred oral anticonvulsant to ensure appropriate use; in patients 18 years and older as adjunct treatment when previous treatment with other AEDs has not provided adequate response or has not been tolerated.
- Continue to prefer generic alternatives where appropriate.

Reason for Review:

In September 2010, the Oregon Health Resources Commission (HRC) evaluated the comparative effectiveness evidence of the oral anticonvulsants. A December 2009 Provider Synergies Review[1] was used as the evidence source. Since this review, a new drug has been approved by the FDA as adjunctive treatment of partial-onset seizures in patients aged 18 years and older (ezogabine).[2] Ezogabine is the first potassium channel opener antiepileptic drug (AED) approved by the FDA. In addition, the Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review evaluating the effectiveness and safety of antiepileptic medications in patients with epilepsy.[3] The National Institute for Health and Clinical Excellence (NICE) published a pharmacological update of clinical guideline 20 regarding the management of epilepsies in adults and children in primary and secondary care.[4, 5] Therefore, this review will focus on the use of oral anticonvulsants in the treatment of epilepsy.

Previous HRC Conclusions (April 2010):

- Evidence does not support a difference in efficacy/effectiveness (Grade B).
- Evidence does not support a difference in harms/adverse events (Grade B).
- Felbamate is not indicated as first line antiepileptic
- Vigabatrin is the only agent indicated for treatment of infantile spasm
- Consideration of “Grandfather” the chemical entity for epilepsy diagnoses.
- Consider inclusion of all agents for epilepsy diagnoses

- Consider PA criteria/quantity limit for diazepam rectal gel
- Consider PA vigabatrin for appropriate populations.

Background:
Epilepsy is a common neurological disorder characterized by recurring epileptic seizures. Antiepileptic drugs (AEDs) to prevent recurrence of seizures are the mainstay of treatment.[5] There are between 16 and 51 cases of new-onset epilepsy per 100,000 people every year and over a lifetime, approximately 10 percent of people in the United States will suffer a seizure.[6,3] The three main types of seizures in patients include partial, generalized, and unclassified. The overall goals of antiepileptic therapy are to prevent seizures and avoid unnecessary side effects with a drug regimen that is relatively convenient.[3] People usually begin treatment with one medication, but many will become refractory to this medication. It is estimated that up to 22.5% of patients have drug-resistant epilepsy.[6] Selecting an effective drug with the least potential for side effects is a critical decision for clinicians. Since 1993, the FDA has approved several newer AEDs and it has been a continued interest to compare the effectiveness and safety of the newer AEDs to the older AEDs. Another concern in the management of epilepsy is the continued controversy surrounding the practice of generic substitution of innovator AEDs.[3] Seizure freedom is commonly the most important outcome and goal of treatment, although reduction in seizure frequency of 50% or more is generally accepted as demonstrating efficacy for FDA approval.[4,6] When initial drugs have failed and adjunctive treatment is used seizure reduction is likely to be the primary aim.

Methods:
A Medline literature search ending April 2012 for new systematic reviews and randomized controlled trials (RCT's) comparing medications head-to-head in the treatment of epilepsy was conducted. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

New Guidelines:
NICE updated the 2004 guideline on the management of the epilepsies in adults and children with regard to drug management (January 2012).[4] A literature search was performed and updated at 6 weeks before the end of guideline development. The evidence for outcomes were assessed for quality and presented using an adaption of Grading of Recommendations Assessment, Development, and Evaluation (GRADE) toolbox. The majority of the new recommendations are based on moderate to very low quality evidence from randomized controlled trials and the opinion of the guideline development group. General and new 2012 recommendations were:

- It is recommended that combination therapy (adjunctive or 'add-on' therapy) should only be considered when attempts at monotherapy with AEDs have not resulted in seizure freedom. If trials of combination therapy do not bring about worthwhile benefits, treatment should

revert to the regimen (monotherapy or combination therapy) that has proved most acceptable to the child, young person or adult, in terms of providing the best balance between effectiveness in reducing seizure frequency and tolerability of side effects.

- If an AED has failed because of adverse effects or continued seizures, a second drug should be started (which may be an alternative first-line or second-line drug) and built up to an adequate or maximum tolerated dose and then the first drug should be tapered off slowly.
- If using carbamazepine, offer controlled-release preparations (new 2012) due to similar efficacy and a better adverse effect profile (based on consensus opinion).

Focal seizures

- Offer carbamazepine or lamotrigine as first line treatment (based on moderate to very low quality evidence).
- If these are unsuitable or not tolerated, offer an alternative from carbamazepine, lamotrigine, oxcarbazepine, levitiracetam, or sodium valproate (moderate to very low quality evidence).
- If first line treatments are ineffective, offer adjunctive treatment with carbamazepine, clobazam, gabapentin, lamogtrigine, levetiracetam, oxcarbazepine, sodium valproate, or topiramate (moderate to very low quality evidence).

Generalized tonic-clinic seizures

- Offer sodium valproate as first line treatment and if it is unsuitable, offer lamotrigine (low to very low quality evidence). .
- Consider carbamazepine and oxcarbazepine, but be aware of the risk of exacerbating myoclonic or absence seizures.
- If first line treatments are ineffective or not tolerated, offer lamotrigine, levetiracetam, sodium valproate, or topiramate as adjunctive treatment (high to very low quality evidence).

Prolonged or repeated seizures

- Only prescribe buccal midazolam or rectal diazepam for use in the community for those who have had a previous episode of prolonged or serial convulsive seizures (based on consensus opinion).
- Administer buccal midazolam as first line treatment in the community. Administer rectal diazepam if preferred or if buccal midazolam is not available (high to very low quality evidence).

NICE has also issued guidance and a final appraisal determination recommending retigabine (ezogabine) as an option for the adjunctive treatment of partial (the term focal has been used in this guideline) onset seizures with or without secondary generalization in adults aged 18 years and older with epilepsy, when previous treatment with other AEDs (carbamazepine, oxcarbamazepine, sodium valproate, gabapentin, lamotrigine, levitiracetam, and topiramate) has not provided adequate response or has not been tolerated.[7] The Committee also reported that research investigating the health-related quality of life of people with epilepsy would be of value for defining the appropriate use of this medication.

New Systematic Review:

A recent AHRQ comparative effectiveness review was prepared to examine the comparative efficacy, safety, and tolerability of the newer versus older and innovator versus generic AEDs.[3] A literature search was conducted through March 23, 2011 and each study was assessed for validity and rated as good, fair, or poor. Newer versus older comparisons were largely limited to studies using carbamazepine or valproic acid and to a lesser extent phenytoin and sustained/controlled-release carbamazepine. Comparisons versus clonazepam, phenobarbital, ethosuximide, or primidone

were very limited or not conducted at all. Newer versus older comparisons were also largely limited to gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate and vigabatrin.[3] Comparisons versus felbamate, lacosamide, pregabalin, tiagabine, and zonisamide were very limited or not conducted at all. Innovator versus generic antiepileptic medication comparisons are limited predominantly to studies of carbamazepine and to a lesser extent phenytoin and valproic acid. The use of an "A" rated generic could only be verified in one controlled clinical trial and a minority of controlled observational studies. General conclusions were:

- Patients given newer antiepileptic medications were less likely to be seizure free for 6–12 months or 24 months and had a greater risk of withdrawing due to a lack of efficacy than those receiving carbamazepine.
- There was low strength of evidence that there is no difference in mortality between newer AED's compared to carbamazepine, phenytoin, or valproic acid (RR 0.75; 95% CI 0.51 to 1.12, RR 0.30; 95% CI 0.05 to 195, RR 0.94; 95% CI 0.31 to 2.80 respectively)
- Patients receiving newer antiepileptic medications were more likely to withdraw due to a lack of efficacy than those receiving carbamazepine sustained or controlled release products but newer medications were also more likely to withdraw due to adverse events and skin rash (low to insufficient strength of evidence) compared to carbamazepine products.
- There was low to moderate strength of evidence that there was no significant difference in the risk of being seizure free for the study duration when newer antiepileptic medications were compared against phenytoin or valproic acid, or the risk of being seizure free at 6–12 or 24 months for valproic acid.
- No significant differences were seen for newer antiepileptic medications versus either phenytoin or valproic acid for withdrawals for any reason, withdrawals due to lack of efficacy, or withdrawals due to adverse events.
- There was high strength of evidence that the risk of gum hyperplasia was reduced with newer AEDs compared to phenytoin (RR 0.10; 95% CI 0.04 to 0.27, NNT 6).
- For the comparison of innovator antiepileptic medications to their respective generic versions, we found that seizure occurrence (low strength evidence), seizure frequency, total withdrawals, withdrawals due to lack of efficacy, or withdrawals due to adverse events were not significantly different in controlled clinical trials.
- There was insufficient to low strength of evidence (using data from observational studies), that switching from an innovator to a generic, generic to generic, or generic to innovator version of the same antiepileptic medication may increase the short-term risk of hospitalization, hospital stay duration, and the short-term risk of a composite of medical service utilization but may not increase outpatient service utilization.

New Drug Evaluation: Ezogabine (Potiga®)

FDA Indication:
Ezogabine is a potassium channel opener indicated as adjunctive treatment of partial-onset seizures in patients aged 18 years and older. Ezogabine is administered in 3 divided daily doses. Initial dosage should be 100 mg 3 times daily for 1 week, titrating to maintenance dose at weekly intervals

by no more than 150 mg per day. The optimal effective dosage is between 600 mg/day and 1200 mg/day. In the clinical trials however, 1200 mg /day showed limited improvement compared to 900 mg/day with an increase in adverse reactions and discontinuations.

Potential Off-label Use:
Although not FDA-approved, ezogabine has been studied in post-herpetic neuralgia and bipolar disorder. The limited evidence demonstrated no significant improvement in efficacy in either off-label use.[8]

Clinical Efficacy:
Ezogabine was approved based on three double-blind fair quality studies (two 16-week[9,10] and one 18-week[11]) involving 1,239 patients with inadequately controlled partial-onset seizures already receiving 1-3 AEDs. The studies evaluated doses from 600mg – 1200mg. In one fair quality dose-ranging study, ezogabine 900mg/day and 1200mg/day demonstrated a statistically significant reduction in the total partial seizure rate compared to placebo (-29.3% in 900mg/day arm, -35.2% in 1200mg/day arm, and -13.1% in placebo; p=0.0387 and 0.0024, respectively).[10] These treatment groups also showed a significantly higher responder rate, defined as ≥50% reduction in 28-day rate of seizures (900mg/day: 31.6%, 1200mg/day: 33%, placebo: 15.6%; p=0.0214 and 0.016, respectively).[10] Ezogabine 600mg/day did not reach statistical significance for either endpoint.

Two additional fair quality placebo controlled efficacy trials were also evaluated for drug approval (RESTORE 1 and RESTORE 2).[9,11] RESTORE 1 was a fair quality, 18-week study. Participants taking ezogabine 1200mg/day demonstrated a significant improvement in reduction in seizure frequency compared to placebo (-44.3% vs. -17.5%, p<0.001) and a greater responder rate (44.4% vs. 17.8%, RR 2.5; 95% CI 1.7 to 3.8, p<0.001). There was no significant difference in the proportion of patients who were seizure free (2% vs.)%, p=0.083). In this study, there was an unequal distribution in the two groups regarding percentage of patients on 1, 2, or 3 concurrent AEDs.

RESTORE 2 was a fair quality 16 week study. Ezogabine 600mg/day and 900mg/day were shown to significantly improve the change in partial seizure frequency compared to placebo (-27.9% vs. -39.9% vs. -15.9%, for 600mg/day, 900mg, and placebo; p<0.007 and <0.001 respectively). Both doses also demonstrated a significant increase in responder rate compared to placebo (600mg/day 32% vs. placebo 17%, RR 1.9; 95% CI 1.2-2.9, p=0.002 and 900mg/day 39% vs. placebo 17%, RR 2.4; 95% CI 1.7 to 3.6, p<0.001). The proportion of patients who were seizure free was not reported in RESTORE 2.

All studies showed a statistically significant increase in withdrawal due to adverse events with ezogabine compared to placebo with rates of discontinuation due to adverse events ranging from 14.4% to 29.2% and appeared to be dose-related (25% across all three studies for ezogabine vs. 11% for placebo). The two studies that reported total attrition rates also demonstrated higher total dropout rates with treatment compared to placebo. The most common adverse reactions leading to withdrawal were dizziness (6%), confusional state (4%), fatigue and somnolence (3%). In the clinical trials, dizziness was reported in 23% of patients treated with ezogabine compared to 9% of patients on placebo. Confusional state,

psychotic symptoms and hallucinations were reported more frequently in patients treated with ezogabine than in those treated with placebo in the clinical trials (9% of ezogabine participants experienced a confusional state versus 3% in the placebo group). Ezogabine also caused urinary retention in clinical trials. In trials, "urinary retention, urinary hesitation and dysuria were reported in 0.9%, 2.2%, and 2.3% of patients on ezogabine, respectively, and in 0.5%, 0.9%, and 0.7% of patients on placebo, respectively.

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) Proportion of seizure free patients
2) Proportion of participants experiencing at least a 50% reduction in seizure frequency (responders)
3) Quality of Life
4) Withdrawals

Primary Study Endpoint:

1) Percent change in 28-day total partial seizure frequency

Ref./ Study Design[a]	Drug Regimens	Patient Population	N	Duration	Efficacy Results[b]	ARR / NNT[c]	Safety Results (CI, p-values)	ARI / NNH	Quality Rating[d]; Comments
RESTORE 1									Fair;
French et. al. Phase III, RCT, DB, PC	T: Ezogabine 1,200mg/day w/background therapy of 1-3 AEDs and/or vagus nerve stimulation C: Placebo + Background therapy of 1-3 AEDs and/or vagus nerve stimulation	Mean Age: 37 yrs Male: 46% White: 54% Drug resistant partial epilepsy patients w/ or without 2° generalizations currently on 1-3 AED's and/or vagus nerve stimulation	T: 153 C: 152	Outcomes assessed @ 18 weeks Trial consisted Of 8 wk baseline phase + 6 wk dose titratio phase + 12 weeks maintenance phase	<u>% Δ in 28-day seizure frequency at week 18:</u> T: -44.3% C: -17.5% P=<0.001 <u>% patients w/ ≥50% in seizure frequency over 28 days:</u> T: 68 (44.4%) C: 27 (17.8%) RR 0.4 95% CI 0.26 to 0.59 P=<0.001 <u>Patients who were seizure free</u> T: 3 (2%) C: 0 (0%) P=0.083 RR 0; 95% CI 0 to 2.25	NA ARR: 26.6% NNT: 4 NS	<u>Withdrawals due to Adverse events:</u> T: 41 (26.8%) C: 13 (8.6%) P<0.001 RR:3.12 95% CI (1.7-5.9)	ARI: 18.2% NNH:	• Placebo group had a higher % of pts on 3 AEDs 40.5% vs 27.5% in EZG group, while EZG group had more patients on 1 or 2 AED's in the than placebo (71.6% vs. 59.9%) • Total attrition rates: o T: 56 (36.6%) o C: 26 (17.1%) • Appropriate randomization, allocatio concealment, and blinding of patient and caregiver • Intention to treat (ITT) included all patients who received at least 1 dose of study drug • LOCF used for missing data
Restore2									
Brodie et. al. Phase III, RCT, DB, PC	T1: Ezogabine 600mg/day T2: Ezogabine 900mg/day C: Placebo	Mean Age: 37 yrs Male: 48% White: 52% Drug resistant epilepsy currently on 1-3 AED's and/or vagus nerve stimulation, >=4 seizures/ 28 days, and without a seizure-free period of more than 21 days Exclusion = CrC <50 ml/min,	T1: 181 T2: 178 C: 179	Outcomes assessed @ 16 weeks Trial consisted Of 8 wk baseline phase + 4 wk dose titratio phase + 12 weeks maintenance phase	<u>% Δ in 28-day seizure frequency:</u> T1: -27.9% T2: -39.9% C: -15.9% P=<0.007, T1 vs. C P=<0.001, T2 vs. C <u>% patients w/ ≥50% in seizure frequency during the maintenance phase:</u> T1: 57 (32%) T2: 70 (39%) C: 31 (17%) P=0.002, T1 vs. C RR 1.9; 95% CI (1.2-2.9) P<0.001, T2 vs. C RR 2.4; 95% CI (1.7 to 3.6)	NA T1 v C ARR: 15% NNT: 7 T2 v C ARR: 22% NNT: 5	<u>Withdrawals due to Adverse events:</u> T1: 26 (14.4%) P=0.049 T2: 46 (25.8%) P=0.049 C: 14 (7.8%) T1 RR:1.8 T2 RR:3.3	T1 AR 6.6% T1 NNH: 6 T2 AR 18 T2 NNH:	Fair; • Randomization stratified by baseline partial seizure frequency per 4 weeks and geographic region • Allocation concealment using interactive voice response system • Blinding of care giver and patient • The most common individual AEDs were also reported. • Total attrition rates: o T1: 46 (25%) o T2: 56 (31%) o C: 27 (15.0%) • Intention to treat (ITT) included all patients who received at least 1 dose of study drug

Porter et. al. Phase III, RCT, DB, PC	T1: Ezogabine 600mg/day T2: Ezogabine 900mg/day T3: Ezogabine 1200mg/day C: Placebo	Mean Age: 36 yrs Male: 52% White: 48% Drug resistant partial epilepsy on stable doses of 1-2 AEDs , no 30-day seizure free period	T1: 99 T2: 95 T3: 106 C: 96	Outcomes assessed @ 16 weeks Trial consisted Of 8 wk baseline phase + 8 wk dose titratio phase + 8 week maintenance phase	<u>Median change in monthly seizure frequency from baseline:</u> T1: -23.4% T2: -29.3% T3: -35.2% C: -13.1% P=NS; T1 v C P=0.0387; T2 v C P=0.0024; T3 v C <u>% patients w/ ≥50% in seizure frequency (responder rate):</u> T1: 23 (23.2%) T2: 30 (31.6%) T3: 35 (33.0%) C: 15 (15.6%) <u>T1 v C</u> RR 1.5; 95% CI (0.8-2.8) P=NS <u>T2 v C</u> RR 2.0; 95% CI (1.1 to 3.7) p=0.0214 <u>T3 v C</u> RR2.1; 95% CI (1.2 to 3.8) P=0.016	N/A T1 : NS T2 ARR: 16% NNT: 7 T3 ARR: 17.4% NNT:6	<u>Withdrawals due to Adverse events:</u> T1: 17 (17%) P=0.361 T2: 19 (20%) P=0.161 T3: 31 (29.2%) C: 12 (12.5%) P=0.004	T1 AR NS T2 AR NS T3 ARI:18 5% T3 NNH:6	Fair; • Blinded to patient and care provider, no information on outcome assessor • Intention to treat (ITT) included all patients who received at least 1 dose of study drug, had a baseline seizure evaluation, and at least one evaluatio during the double-blind treatment phase (only excluded 3 patients) • Missing data imputed based on the assumption that seizures are uniformly distributed over time • During titration phase, the target dos was only reached in 50% of the patients in the 1200mg/day arm

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)

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Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY : The exact mechanism of action of ezogabine is not fully known. It is thought to enhance potassium channels and stabilize the resting membrane potential, thereby reducing brain excitability. It may also have some effects on GABA-mediated currents. The QTc prolongation risk was evaluated in healthy subjects and the maximum mean increase of QTc interval was 7.7 msec.

PHARMACOKINETICS[1]

Parameter	Result
Oral Bioavailability	60%
Protein Binding	80% bound to plasma protein
Elimination	Major route of elimination is renal excretion, about 85% of dose recovered in the urine
Half-Life	7 to 11 hours
Metabolism	primarily via glucuronidation and acetylation. Studies have shown no metabolism by the cytochrome P450 enzymes.

DOSE & AVAILABILITY[1]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
Ezogabine 50mg, 200 mg, 300 mg, 400 mg	Oral	three times daily	Initial dose : 100 mg three times daily (300 mg per day) Increase by no more than 50 mg 3 times daily, at weekly intervals Maximum	<u>CrCl < 50 ml/min or ESRD:</u> Initial dose: 50 mg 3 times daily (150 mg per day) Maximum dose: 200 mg 3 times daily (600 mg per day)	<u>Child-Pugh 7-9:</u> Initial dose: 50 mg 3 times daily (150 mg per day) Maximum dose: 250 mg 3 times daily (750 mg per day) <u>Child-Pugh >9:</u> Initial dose: 50 mg 3 times daily (150 mg per day)	The safety and effectiveness in patients < 18 years old has not been established.	(patients > 65y/o) Initial dose: 50 mg 3 times daily (150 mg per day) Maximum dose: 250 mg 3 times daily (750 mg per day)	Can be taken with or without food.

			dose: 400 mg 3 times daily (1200 mg per day)		Maximum dose: 200 mg 3 times daily (600 mg per day)			

DRUG SAFETY[1]

Serious (REMS, Black Box Warnings, Contraindications): None

Warnings and Precautions:

Urinary Retention: Ezogabine caused urinary retention in clinical trials in approximately 2% of treated patients. Urologic symptoms should be carefully monitored, especially in those who have other risk factors for urinary retention.

Neuro-Psychiatric Symptoms: Confusional state, psychotic symptoms, and hallucinations were reported more frequently than placebo in clinical trials. Discontinuations from these were reactions were more common in the treated group than the placebo group. Half of the patients who discontinued due to hallucinations or psychosis required hospitalization. Rapid titration at greater than the recommended doses appeared to increase the risk of psychosis and hallucinations.

Dizziness and Somnolence: Ezogabine causes dose-related increases in dizziness and somnolence.

QT Interval Effect: A study showed that ezogabine produced a mean 7.7 msec QT prolongation in healthy volunteers. 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.

Suicidal Behavior and Ideation: Antiepileptic drugs, including ezogabine, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with ezogabine should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.