

Brand Name: Potiga™

Generic Name: Ezogabine

Manufacturer: Valeant Pharmaceuticals International

Drug Class^{1,2,3,4}: Anticonvulsant, Neuronal Potassium Channel Opener

Uses^{1,2,3,4}:

Labeled Uses: Adjunct treatment of partial-onset seizures

Mechanism of Action^{1,2,3,4}: Opens potassium channels (KCNQ2-KCNQ5 [Kv7.2-Kv7.5]) and activating the M current.

Pharmacokinetics^{1,2,3,4}

Absorption:

T _{max}	0.5-2 hours, delayed by 0.75h by high-fat meal
V _d	2-3 L/kg
t _{1/2}	7-11 hours, increased by 30% in elderly
Clearance	Not reported
Protein Binding	80% for ezogabine, 45% for active metabolite NAMR
Bioavailability	~60%

Metabolism: Ezogabine is primarily metabolized in the liver via glucuronidation by enzymes UGT1A4, UGT1A1, UGT1A3, and UGT1A9 and via acetylation through enzyme NAT2.

Elimination: Ezogabine is eliminated in both urine (~85%; 36% as unchanged drug, 18% as primary metabolite, NAMR) and feces (~14%, 3% as unchanged drug).

Efficacy:

French, J.A., Abou-Khalil, B.W., et al. Randomized, double-blind, placebo-controlled trial of ezogabine (retigabine) in partial epilepsy. Neurology. 2011 May 3; 76(18): 1555-63.

Study Design: Multicenter, randomized, double-blind, parallel-group study.

Description of Study: *Methods:* Three-hundred-six men and women aged 18-75 from 53 centers in the United States, Canada, Mexico, Argentina, and Brazil were randomized to receive either ezogabine 1200mg/day or placebo. Subjects underwent an 8-week prospective baseline phase followed by an 18-week double-blind treatment phase (6-week titration phase, 12-week maintenance). Background antiepileptic drugs (AEDs) or their use of vagus nerve stimulators (VNSs) settings were kept stable during the study. Patients or caregivers recorded seizure type and frequency, adverse events (AEs), and concomitant treatment in daily diaries. Patients were

randomized 1:1 to ezogabine 400mg TID (after a 6-week titration) or placebo. The two primary endpoints of the study were percent change in 28-day total partial-seizure frequency from baseline to week 18 and responder rate. Secondary endpoints were distribution of patients across seizure frequency reduction categories, proportion of seizure-free patients, percent of treatment days without seizures, and Clinical/Patient global Impressions of Improvement. Results were analyzed on an intent-to-treat (ITT) basis for the entire 18-week period and for patients reaching maintenance phase. *Outcome Results:* The median percent reduction in total partial-seizure frequency was 44.3% and 17.5% ($p < 0.001$) for ezogabine and placebo respectively. Responder rates were 44.4% and 17.8% ($p < 0.001$) for ezogabine and placebo respectively. Similar results were reported for reduction in seizure activity and response rate for the 12-week maintenance phase. Patients discontinuing treatment due to AEs were 26.8% (ezogabine) v. 8.6% (placebo). The most common adverse events were dizziness, somnolence, fatigue, confusion, dysarthria, UTI, ataxia, and blurred vision.

Limitations: Study was sponsored by Valeant Pharmaceuticals International, manufacturer of ezogabine. Many of the authors have received research support from or have been employed by Valeant. Study subjects were only reported as white, hispanic, or black, so effectiveness of drug in other races not evaluated. The standardization of daily diaries between sites was not addressed. Also, accuracy of diaries may be questionable since patients or caregivers were required to fill them out. Only 63% of subjects receiving ezogabine completed the double-blind treatment, with 27% of the ITT population discontinuing study due to adverse events.

Conclusion: The results of this study show that ezogabine is useful in treating partial-onset seizures. However, adverse reactions to the drug limits its overall usefulness, as 41 (26.8%) of the patients who entered the maintenance phase of the study discontinued due to adverse reactions. More research must be conducted at doses lower than 1200mg/day in order to assess response rate and adverse effect profile.

Brodie, M.J., Lerche, H. et al. Efficacy and safety of adjunctive ezogabine (retigabine) in refractory partial epilepsy. *Neurology*. 2010 Nov 16; 75(20): 1817-24.

Study Design: Multicenter, randomized, double-blind, placebo-controlled trial.

Description of Study: *Methods:* Five-hundred-thirty-eight patients comprising the ITT population were randomized into 3 groups, with 179 receiving placebo, 181 receiving 600mg ezogabine, and 178 receiving 900mg ezogabine. Patients 18-75 years old with an established diagnosis of localization-related epilepsy refractory to 1-3 AEDs were drawn from 71 centers in the US, Europe, and Australia. The study consisted of four phases, a prospective 8-week baseline, 4-week titration, 12-week maintenance, and 4-week transition phase for patients electing to take part in an open-label extension. Primary outcome measure was change in 28-day seizure frequency, measured by daily diary. The primary endpoint for the FDA was change in total partial seizure frequency per 28 days from baseline to double-blind period, while for EMEA it was proportion of responders from baseline to maintenance for. *Outcome Results:* For the

ITT FDA endpoint, reduction in seizure frequency was higher for both 600mg/d (27.9%, $p=0.007$) and 900mg/d (39.9%, $p<0.001$) v. placebo (15.9%). For the ITT EMEA endpoint, responder rate was higher for both 600mg (38.6%, $p<0.001$) and 900mg/d (47%, $p<0.001$) v. placebo (18.9%). Adverse events were reported by 66% of placebo patients, 73% of ezogabine 600mg/d patients, and 79% of ezogabine 900mg/d patients; the most common were dizziness, somnolence, headache, and fatigue. The numbers of patients discontinuing study due to AEs were 8% for placebo, 17% for ezogabine 600mg/d, and 26% for ezogabine 900mg/d. The most common reasons were dizziness and somnolence.

Limitations: Study was sponsored by Valeant Pharmaceuticals International, manufacturer of ezogabine. Many of the authors have received research support from or have been employed by Valeant. For the primary efficacy endpoints, neither Standard deviation (SD) nor Confidence Intervals (CI) were reported. Data may not be reliable as patients filled out daily diaries, with no mention of standardization across sites. The duration of the study may be too short to see significant results. Authors did not discuss in much detail the impact of adverse events, even though 46 out of 178 patients in the 900mg/d group discontinued treatment because of adverse events. Also, comparisons of adverse events between groups were not statistically analyzed.

Conclusion: Based on the results of this study, 600mg/d of ezogabine appears to be a safe and useful as adjunct therapy for refractory partial seizures. The 900mg/d dose should be used cautiously as the high incidence of adverse events in this group limits clinical significance. The reduction in seizure activity versus placebo for 600mg/d was statistically significant and this dose showed a much lower rate of discontinuation due to adverse events than 900mg/d.

Porter, R.J., Partiot, A., et al. Randomized, multicenter, dose-ranging trial of retigabine for partial-onset seizures. *Neurology*. 2007 Apr 10; 68(15): 1197-204.

Study Design: Multicenter, randomized, double-blind, placebo-controlled trial.

Description of Study: *Methods:* Patients were enrolled from 73 centers in 19 countries in Europe, Australia, and the US. A total of 537 patients were screened for the ITT populations of 99 for placebo, 99 for ezogabine 600mg/d, 95 for ezogabine 900mg/d, and 106 for ezogabine 1200mg/d. The study consisted of a prospective 8-week baseline phase, an 8-week forced titration phase, and an 8-week maintenance phase. Eligible patients were 16-70 year olds who had inadequately controlled partial-onset seizures, defined as occurring at least 4 times during the 8-week baseline phase with no 30-day seizure-free period. Seizures were recorded by patients using a daily diary. Investigators calculated monthly seizure rate from patient diaries. Efficacy measures were performed on the ITT population. The primary efficacy outcome was the median percent change in monthly total partial seizure frequency during the double-blind treatment compared with baseline seizure frequency. Secondary outcomes were responder rate and clinical global improvement score. *Outcome Results:* The median percent change in monthly partial seizure frequency from baseline was -23% for 600mg/d (p not specified), -29% for 900mg/d ($p=0.0387$), -35% for 1200mg/d ($p=0.0024$), and -13% for placebo. Reduction in

seizure activity was dose-dependent ($p < 0.001$). The difference between placebo and 600mg/d was not significant. The responder rate was 23% (p not specified) for 600mg/d, 32% ($p = 0.0214$) for 900mg/d, 33% ($p = 0.0214$) for 1200mg/d, and 16% for placebo.

Limitations: Some of the authors have received research support from or have been employed by Valeant Study subjects were overwhelmingly white, limiting the ability of the results of this study to be generalized to other races. Use of patient diaries was not stated to be standardized across study sites, which may provide unreliable data for study outcomes. SD was not provided for primary or secondary outcome, giving no information regarding variability of individual patients. Not much discussion was given to adverse events. Information on adverse events also not clearly presented.

Conclusion: Based on the results of this study, ezogabine at 900mg/d or 1200mg/d appears to be useful in treating refractory partial seizures. These doses showed significant improvement over placebo in both primary and secondary outcome measures, and adverse events did not appear to be an issue. However, the true safety of these doses may not be reflected by the study. The number of adverse events and dropouts are reported as number of events, not number of patients experiencing those events.

Contraindications^{1,2,3,4}: No specific contraindications have been determined.

Precautions^{1,2,3,4}:

Abrupt Withdrawal: May increase seizure frequency.

Congestive Heart Failure: QT-prolongation reported within 3 hours of administration; QT interval should be monitored.

Age: Over 65 years old, dose adjustment needed.

Hepatic Impairment: Severe or moderate (Child-Pugh > 7) dose adjustment required.

Hypokalemia: QT-prolongation reported within 3 hours of administration; QT interval should be monitored.

Hypomagnesemia: QT-prolongation reported within 3 hours of administration; QT interval should be monitored.

Renal Impairment: CrCl <50 ml/min, dose adjustment required.

Suicidal Thoughts and Behavior: Have been reported as early as 1 week following initiation. Monitor and evaluate risk/benefit of continued use.

Urinary Retention: May require catheterization, and possibly continued catheterization, following discontinuation; increased risk in patients with concomitant risk factors (e.g., benign

prostatic hyperplasia, especially elderly), inability to communicate symptoms (e.g., cognitive impairment), and with concomitant use of other drugs that affect voiding (e.g., anticholinergics)

Ventricular Hypertrophy: QT-prolongation reported within 3 hours of administration; QT interval should be monitored.

Adverse Effects²:

In > 10% of patients

Central Nervous System

- Dizziness – 23%
- Somnolence – 22%
- Fatigue – 15%

In 2-10% of patients

Central Nervous System

- Confusion – 9%
- Vertigo – 8%
- Coordination Impairment – 7%
- Attention Disturbance – 6%
- Memory Impairment – 6%
- Aphasia – 4%
- Balance Disorder – 4%
- Anxiety – 3%
- Amnesia – 2%
- Disorientation – 2%

Gastrointestinal

- Nausea – 7%
- Constipation – 3%
- Weight Gain – 3%
- Dysphagia – 2%

Ocular

- Diplopia – 7%
- Blurred Vision – 5%

Neuromuscular & Skeletal

- Tremor – 8%
- Weakness – 5%
- Abnormal Gait – 4%
- Dysarthria – 4%
- Paresthesia – 3%

Renal

Chromaturia – 2%
Dysuria – 2%
Hematuria – 2%
Urinary Hesitation – 2%

Miscellaneous

Influenza Infection – 3%

In < 2% of patients

Alopecia, appetite increase, coma, dyspnea, encephalopathy, Euphoria, hallucinations, hydronephrosis, hyperhidrosis, hypokinesia, leukopenia, liver enzymes increased, malaise, muscle spasms, myoclonus, nephrolithiasis, neutropenia, nystagmus, peripheral edema, psychotic disorder, rash, renal colic, syncope, thrombocytopenia, urinary retention, xerostomia

Drug Interactions^{1,3}

Coadministration with drugs that prolong QT interval

abarelix, alfuzosin, amiodarone, amoxapine, apomorphine, arsenic trioxide, artemether, asenapine, astemizole, bepridil, beta-agonists, bretylium, chloroquine, chlorpromazine, cisapride, citalopram, clarithromycin, clozapine, cyclobenzaprine, dasatinib, dextromethorphan, disopyramide, dofetilide, dolasetron, dronedarone, droperidol, erythromycin, flecainide, fluoroquinolones, fluphenazine, halofantrine, halogenated anesthetics, haloperidol, ibutilide, iloperidone, lapatinib, levomethadyl, local anesthetics, lopinavir, lumefantrine, magnesium sulfate, maprotiline, mefloquine, mesoridazine, methadone, nilotinib, octreotide, olanzapine, ondansetron, paliperidone, palonosetron, pentamidine, perphenazine, pimozide, posaconazole, potassium sulfate, probucol, procainamide, prochlorperazine, propafenone, quetiapine, quinidine, quinidine, ranolazine, risperidone, ritonavir, saquinavir, sertindole, sodium sulfate, sotalol, sunitinib, tacrolimus, telavancin, telithromycin, terfenadine, tetrabenazine, thioridazine, tricyclic antidepressants, trifluoperazine, troleandomycin (based on interactions with macrolides), vardenafil, venlafaxine, vorinostat, ziprasidone

May result in additive prolongation of QT interval.

Carbamazepine (Major)

May result in decreased ezogabine plasma concentrations due to induction of the uridine diphosphate glucuronidation pathway by carbamazepine. Consider increasing ezogabine dose while on carbamazepine.

Phenytoin (Major)

May result in decreased ezogabine plasma concentrations due to induction of the uridine diphosphate glucuronidation pathway by phenytoin. Consider increasing ezogabine dose while on phenytoin.

Lamotrigine (Major)

May result in decreased lamotrigine plasma concentrations. Mechanism unknown.

Digoxin (Major)

May result in increased digoxin serum concentrations because of concentration-dependent inhibition of P-glycoprotein transport and inhibition of renal clearance of digoxin by NMAR. Monitor serum digoxin levels.

Drugs that affect voiding

antimuscarinics, sedating H1-blockers, amantadine

Dosing/Administration^{1,2,3,4}:*Adult*

Begin at 100mg 3 times/day. Increase by no more than 50mg 3 times/day (150mg/d) at weekly intervals to maintenance dose of 200-400mg 3 times/day.

Pediatric

Safety and efficacy has not been established in children.

Elderly

Initial dose of 50mg 3 times/day. Increase by 50mg 3 times/day (150mg/d) at weekly intervals to maximum dose of 250mg 3 times/day.

Renal Impairment (CrCl <50 ml/min)

Initial dose of 50mg 3 times/day. Increase by 50mg 3 times/day (150mg/d) at weekly intervals to maximum dose of 200mg 3 times/day.

Hepatic Impairment (Moderate, Child Pugh 7-9)

Initial dose of 50mg 3 times/day. Increase by 50mg 3 times/day (150mg/d) at weekly intervals to maximum dose of 250mg 3 times/day.

Hepatic Impairment (Severe, Child Pugh >9)

Initial dose of 50mg 3 times/day. Increase by 50mg 3 times/day (150mg/d) at weekly intervals to maximum dose of 200mg 3 times/day.

Hemodialysis

Initial dose of 50mg 3 times/day. Increase by 50mg 3 times/day (150mg/d) at weekly intervals to maximum dose of 200mg 3 times/day.

Use in Special Circumstances:

Pregnancy Category: C

Breastfeeding: It is unknown if ezogabine is excreted in human milk. However, it has been shown to be excreted in milk by rats.

Monitoring Parameters:

Seizures; electrolytes, bilirubin, ALT, AST, serum creatinine, QT interval; urinary retention; observe patient for excessive sedation, confusion, psychotic symptoms, and hallucinations; suicidality (eg, suicidal thoughts, depression, behavioral changes); evaluate for signs/symptoms of ezogabine toxicity

Conclusion

Ezogabine is an effective adjunctive therapy for patients with refractory partial-onset seizures. Many of the adverse events associated with the drug appear to be dose dependent. This may limit the clinical usefulness of the higher approved doses. At the higher doses studied, many patients discontinued use of ezogabine due to the adverse events. This may lead to the drug being less useful clinically than it appears from the studies. None of the three studies evaluated lasted longer than 18 weeks for the titration and maintenance phases. Ezogabine was not compared to an active adjunct agent in these studies. Because epilepsy is a chronic disease, the duration of these studies may not have been long enough to see the true effect of the drug. Additionally, no study has compared the efficacy of ezogabine when added to known concurrent antiepileptic regimens. This information would be useful in predicting which patients would respond favorably to the addition of ezogabine. Ezogabine is available 50mg, 200mg, 300mg, and 400mg tablets. The pricing and insurance coverage for ezogabine is currently unknown.

References

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