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RESEARCH**

*APPLICATION NUMBER:*

**022345Orig1s000**

**OFFICE DIRECTOR MEMO**

## Deputy Office Director Decisional Memo; Ezogabine – NDA 22-345

<b>Date</b>	6/10/2011
<b>From</b>	Ellis F. Unger, M.D., Deputy Director, ODE-I
<b>Subject</b>	Deputy Office Director Decisional Memo
<b>NDA#</b>	22-345
<b>Applicant Name</b>	Valeant Pharmaceuticals North America
<b>Date of Complete Response Resubmission</b>	4/15/2011
<b>PDUFA Goal Date</b>	6/15/2011
<b>Proprietary Name / Established (USAN) Name</b>	Potiga ezogabine
<b>Dosage Forms / Strength</b>	Oral / 50, 200, 300, and 400 mg
<b>Indication sought</b>	...adjunctive treatment of partial-onset seizures in patients aged 18 years and older.
<b>Action:</b>	<i>Approval</i>

<b>Material Reviewed/Consulted – Action Package, including:</b>	
Project Manager	Karen Abraham-Burrell, Susan Daugherty
Medical Officer Review	Steven Dinsmore
Consultant, Division of Reproductive and Urologic Products	Chong M. Kim, Mark Hirsch
Pharmacometric Review	Joo-Yeon Lee, Yaning Wang
Pharmacogenomic Review	Li Zhang, Issam Zineh
Statistical Review	Ohidul Siddiqui, Ling Chen, Kun Jin
Pharmacology Toxicology	Edward Fisher, Lois Freed
Chemistry Manufacturing and Controls	Mohan Sapru, Martha Heimann, Ramesh Sood
Statistical Review and Evaluation of Carcinogenicity Study	Mohammad Atiar Rahman
Biopharmaceutics	Mohan Sapru, John Duna, Patrick Marroum
Clinical Pharmacology	Ta-Chen Wu, Kristina Dimova, Angela Men
Clinical Pharmacology Safety Review	Peifan Bai, Darrell Abernethy
Environmental Assessment	Mohan Sapru
Division of Scientific Investigations	Antoine El-Hage, Jyoti Patel, Cynthia Kleppinger, Tejashri Purohit-Sheth
Division of Medication Error Prevention and Analysis, Office of Surveillance and Epidemiology	Tara Turner, Zachary Oleszczuk, Manizeh Siahpoushan, Kellie Taylor
Division of Risk Management, Office of Surveillance and Epidemiology	Barbara Fuller, Reema Jain, Mary Dempsey, LaShawn Griffiths, Sharon Mills, Claudia Karwoski, Kendra Worthy, Reema Jain, Jodi Duckhorn, Kate Heinrich
Controlled Substances Staff	Lori Love, Katherine Bonson, Ling Chen, Michael Klein, Silvia Calderon
QT Effects, Interdisciplinary Review Team for QT Studies	Hao Zhu, Jiang Liu, Qianyu Dang, Joanne Zhang, Suchitra Balakrishnan
SEALD Labeling Team	Jun Yan
Division of Drug Marketing, Advertising, and Communications	Meeta Patel
Cross-Discipline Team Leader	Norman Hershkowitz
Director, Division of Neurology Products	Russell Katz

### **Action:**

The Division of Neurology Products is recommending an Approval action on this application, and I concur with their recommendation.

### **Background:**

Ezogabine is a small-molecule, first-in-class, neuronal potassium channel opener. Its purported mechanism of action involves stabilization and enhancement of potassium currents, and therefore differs from that of approved antiepileptic drugs (AEDs). Ezogabine is thought to have little effect on cardiac potassium channels. The proposed use is for adjunctive treatment of partial-onset seizures in patients 18 years of age and older.

Despite the availability of the numerous AEDs for partial onset seizures, there remains a need for new drugs, as some 30% of patients are refractory to conventional treatments and continue to have inadequate seizure control.

Ezogabine was granted marketing authorization in the European Union earlier this year, where the established name is retigabine.

### **Chemistry Manufacturing and Controls (CMC):**

The applicant originally proposed marketing of 50-, (b) (4) 200-, 300-, and 400-mg strength immediate-release film-coated tablets. They performed a bioequivalence study comparing the 400-mg tablet used in the clinical development program with the 400-mg to-be-marketed tablet, and found them bioequivalent. The applicant requested a waiver for bioequivalence studies for the lower strengths of the to-be-marketed tablets, based on dissolution data. Dr. Duan concluded that waivers could be granted for all but the (b) (4), because (b) (4)

(b) (4) In their resubmission, the applicant has addressed this deficiency (b) (4) from the NDA, and agreeing to market only the 50-, 200-, 300-, and 400-mg tablet strengths, an action deemed adequate by the CMC review team.

### **Pharmacology/Toxicology:**

The original review found the application not approvable, because of the presence of (b) (4), a genotoxic impurity, at a level that would exceed the acceptable daily dose of a genotoxic impurity (b) (4) at all proposed therapeutic doses.

The drug substance tested positive in Ames assays, which led the applicant to test for the presence of impurities. They identified 3 impurities of concern in the final product (based on structural alert and/or Ames assay data): (b) (4) and known Ames-positive mutagen, and two (b) (4), both clearly Ames-positive as tested by the applicant. The applicant was able to reduce the specification limits of (b) (4) to acceptable levels (combined, total daily intake (b) (4) however, they provided a specification for (b) (4) of no more than (NMT) (b) (4)). At the maximum proposed daily dose of 1200 mg, this corresponded to a daily exposure of (b) (4), exceeding the acceptable limit by more than (b) (4) of magnitude. They justified the (b) (4) specification on the basis of 3 factors: 1) a lower specification was not achievable; 2) use of an individual TTC (Threshold of Toxicological Concern) approach; and 3) a negative *in vivo* Comet assay.

After weighing of the various factors, the review team opined that the specification of NMT (b) (4) (b) (4) was unacceptable. In essence, the review team did not believe that the negative Comet assay could overcome the concern raised by the positive Ames assay. Moreover, in the days leading up to the PDUFA goal date, the applicant expressed confidence that, through alteration of the (b) (4), they could reduce the concentration of (b) (4). Thus, **the applicant's declaration that a lower specification was not achievable appeared incorrect;** however, no data had been provided to support the manufacturing change.

After considerable discussion, we issued a Complete Response letter on November 30, 2010, mostly on the basis of this issue. The letter communicated that the applicant would need to lower the acceptance limit of (b) (4) to NMT (b) (4), a concentration considered acceptable for a genotoxic impurity at the proposed doses.

In their resubmission, the applicant addressed this deficiency by modifying the drug substance **manufacturing process, lowering (b) (4) impurity levels to NMT (b) (4)** based on a maximum daily dose of 1200 mg.

The decrease in concentration of the (b) (4) impurity was achieved through an (b) (4)

The review team now finds the applicant has addressed all outstanding (b) (4)-related issues in the NDA.

#### Carcinogenicity

**Because of ezogabine's toxicity (see below), the doses used in the carcinogenicity studies were necessarily limited.** Ezogabine was negative in a two-year rat carcinogenicity study, although exposure at the highest dose tested (50 mg/kg/day) was only one-half of that expected under clinical use at a daily dose of 1200 mg. A lifetime mouse carcinogenicity study could not be performed because of urinary bladder toxicity, and so a neonatal mouse carcinogenicity study was **performed – a model thought to be sensitive to genotoxic compounds**, according to Dr. Fisher. In this study, there was a small, dose-related increase in lung neoplasms. (b) (4); was not present in amounts adequate to assess its carcinogenic potential in either carcinogenicity study.

#### Toxicology

Ezogabine caused notable dose-limiting central nervous system (CNS) toxicity in mice, rats, and dogs. Findings included hypoactivity, decreased muscle tone, ataxia, prostration, tremors, convulsions, and myoclonus. Toxicity was greater in neonatal and/or juvenile rodents than adult animals.

KCNQ channels are expressed in urinary bladder smooth muscle cells as well as in neurons, and ezogabine hyperpolarizes the resting membrane potential of isolated rat bladder smooth muscle cells *in vitro*. In animal models of hypertrophic and neurogenic bladder, ezogabine was shown to decrease the frequency of spontaneous bladder contractions and block micturition, respectively. In repeat-dose studies, urinary bladder toxicity was observed in all species when examined. Toxicity was attributed to diminished peristalsis (hypotonic detrusor muscle), leading to bladder distention, and ultimately obstructive uropathy, with renal pelvic dilatation, papillary necrosis, tubular dilatation, degeneration, and regeneration. Toxicity was evident at doses as low as 50 mg/kg (area under the curve [AUC] ~5 mcg·h/mL) in repeat-dose studies in adult mice. In the dose range-

finding study for the neonatal mouse carcinogenicity study, pathologic bladder findings were observed at doses  $\geq 2$  mg/kg.

Ezogabine was found to cause relaxation of the gallbladder smooth muscle *in vitro*, and gallbladder dilatation *in vivo* (by abdominal ultrasound). In chronic dog studies, ezogabine caused localized hepatic damage subjacent to the gallbladder, thought to be caused by mechanical compression. Affected hepatic tissue demonstrated focal pressure necrosis, fibrosis, fibroplasia, mononuclear inflammatory cell infiltration, pigment deposition, and hemorrhage.

### **Clinical Pharmacology:**

Ezogabine is generally rapidly absorbed with two concentration peaks ( $T_{max}$  at 0.67 to 1.5 hours; also 1.7 to 4 hours). Steady-state exposure ( $C_{max}$  and AUC) increased dose-proportionally and linearly at doses up to 400 mg TID. Clearance and half-life were dose-independent, with a half-life of 9 to 14 hours.

**Ezogabine's steady-state volume of distribution is 2-3 L/kg, suggesting wide distribution. The parent drug is 80% protein-bound, (mainly to albumin); NAMR (the N-acetyl metabolite of ezogabine) is 45% protein-bound.**

Ezogabine is eliminated predominately through the kidneys, and approximately 34% is eliminated unchanged in the urine. The drug is metabolized extensively through formation of NAMR and N-glucuronides of both ezogabine and NAMR. There is no evidence of hepatic oxidative metabolism of ezogabine or NAMR via CYP450 enzymes.

In subjects over 65 years of age, plasma AUC values were approximately 40-50% higher than in younger subjects. The review team concluded that the label should recommend dose-reduction by one-third in patients aged 65 and over.

Because of reduced elimination in patients with hepatic impairment, the review team recommended dose-reduction in such patients.

In patients with creatinine clearance  $< 50$  mL/min and patients with end-stage renal disease receiving dialysis, the initial and maintenance doses of ezogabine should be reduced by 50%.

These recommended dose-adjustments will be conveyed in a table in the package insert.

### **Site Inspections:**

GCP compliance issues were identified at one site in study 205 (out of a total of 73). The Sponsor performed a sensitivity analysis and, according to Dr. Siddiqui, this revealed similar magnitudes of effects for all treatment groups. DSI concluded from their inspections that overall performance of studies was adequate.

### **Evidence of Effectiveness:**

The applicant submitted the results of three randomized controlled clinical trials in support of efficacy.

Trial 205 was classified as a phase 2 dose-finding trial; trials 301 and 302 were considered the phase 3 pivotal trials. All were international, randomized, double-blind, placebo-controlled, parallel-arm trials that examined the therapeutic effect of ezogabine as adjunctive therapy in adults with partial-onset epilepsy (simple partial seizures and/or complex partial seizures with or without

secondary generalization). Subjects with simple partial seizures as their only seizure type were eligible if seizures had a motor component.

All trials included a prospective baseline period, followed by titration and maintenance phases; subjects had to experience  $\geq 4$  seizures per 28 days during the prospective baseline period for enrollment.

For trial 205, subjects were eligible if receiving up to 2 AEDs at stable doses, whereas in trials 301 and 302, patients could be receiving up to 3 AEDs at stable doses for at least 1 month prior to screening and throughout the study treatment period.

Some key features of the trials are presented in Table 1. All test drugs were to be administered on a TID basis. A single back-titration to 1050 mg/day was permitted in study 301 for subjects unable to tolerate 1200 mg/day. Only Trial 302 had substantial US representation.

**Table 1:** Major features of efficacy trials

	<b>Study 205</b>	<b>Study 301</b>	<b>Study 302</b>
phase	2b	3	3
sponsor	Wyeth	Valeant	Valeant
treatment groups (daily dose)	600, 900, 1200 mg/day, placebo	1200 mg/day, placebo	600, 900 mg/day, placebo
approximate <i>n</i> per treatment group	100	180	150
baseline period	8 weeks	8 weeks	8 weeks
duration of double-blind period	16 weeks	18 weeks	16 weeks
duration of titration	8 weeks	6 weeks	4 weeks
duration of maintenance	8 weeks	12 weeks	12 weeks
age of subjects	16 to 70	18 to 75	18 to 75
Number of background AEDs	$\leq 2$	$\leq 3$	$\leq 3$
locations	Australia, Belgium, Croatia, Czech Republic, Finland, France, Germany, Israel, Italy, Netherlands, New Zealand, Norway, Poland, Portugal, Slovakia, Spain, Sweden, UK, US	Argentina, Brazil, Canada, Mexico, US	Australia, Belgium, France, Germany, Hungary, Israel, Poland, Russia, South Africa, UK, Ukraine, US
percent US subjects	7%	<1%	49%

For all 3 trials, the primary endpoint was the percent change from baseline seizure frequency as calculated from the 28-day total partial seizure frequency. For subjects who discontinued treatment prematurely, the number of seizures reported up to the time of discontinuation was used to calculate the seizure frequency. Subjects who did not have any post-baseline data were excluded from the primary analyses.

- In Trial 205, the primary analysis set was a modified intent-to-treat population of all randomized patients who received  $\geq 1$  dose of study drug, had a baseline seizure evaluation and  $\geq 1$  seizure

evaluation on treatment. A rank analysis of covariance (ANCOVA) was used to analyze the primary endpoint data, with the rank of the baseline monthly seizure rate as a covariate and treatment and center as factors in the model.

- In Trials 301 and 302, the primary analysis set was a modified intent-to-treat population of all randomized patients who received at least one dose of study drug. The primary analysis was a non-parametric rank analysis of covariance, stratified by geographic region and baseline seizure frequency.

Numerous secondary endpoints were considered, but in essence they were merely alternative ways of considering seizures: 1) quartile distribution of change in seizure frequency from baseline; 2) number of patients who achieve total seizure freedom; 3) time without seizures; 4) potential exacerbation of pre-existing seizures or the development of new seizure types; 5) median percent change in 28-day total seizures in the maintenance phase; and 6) responder rate in the double-blind phase as determined by patients with  $\geq 50\%$  reduction from baseline. There was no formal statistical plan to consider multiplicity, rendering interpretation difficult.

Table 2 summarizes the efficacy data from all three studies. FDA analyses are in agreement with those of the applicant. All comparisons to placebo are statistically significant, except for the 600 mg/day group in trial 205 (which does show a trend, however). It is not clear from the statistical review how multiplicity was considered in trials with more than one active treatment group.

**Table 2:** Median % change from baseline in total partial seizure frequency; trials 205, 301, and 302

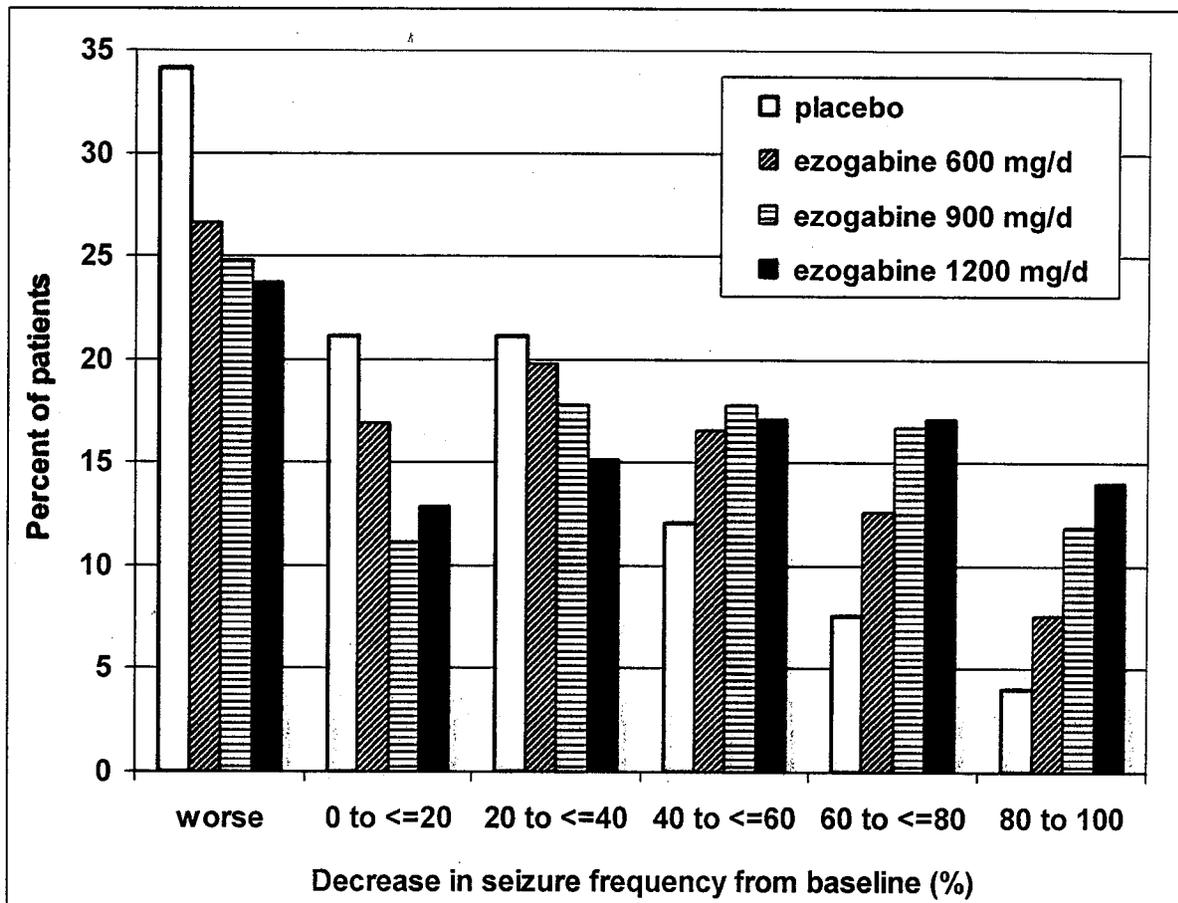
	Placebo	ezogabine 600 mg/day	ezogabine 900 mg/day	ezogabine 1200 mg/day
<b>Trial 205</b>				
n	96	99	95	106
median	-13.1	-23.4	-29.3	-35.2
range	-100, 533	-100, 1703	-100, 298	-100, 375
*p-value	-	0.20	0.043	<0.001
<b>Trial 301</b>				
n	150	-	-	151
median	-17.5	-	-	-44.3
range	-90, 628	-	-	-100, 302
*p-value	-	-	-	<0.001
<b>Trial 302</b>				
n	176	179	175	-
median	-15.9	-27.9	-39.9	-
range	-100, 1712	-94, 250	-100, 226	-
*p-value	-	0.007	<0.001	-

\*p-values from non-parametric rank ANCOVA models

The data provide reasonable if not compelling evidence of a dose-response. Trials 205 and 302 evaluated 2 or 3 ezogabine doses against placebo, and there is fairly clear evidence of a dose-response in both (although in trial 205, the difference between the lowest dose and placebo was not statistically significant). If one succumbs to the temptation to compare results across trials, the

dose-response seems fairly well-characterized, although there are some important assumptions and limitations inherent in doing this.

The figure shows changes from baseline in the 28-day total partial seizure frequency by category for patients treated with various dosing regimens of ezogabine and placebo in an integrated analysis across studies 205, 301, and 302. Patients in whom the seizure frequency increased are shown in the left category as “worse.” Patients in whom the seizure frequency decreased are shown in the five categories at right. Although the limitations of cross-trial comparisons should be kept in mind, the data show that increasing the daily dose from 600 to 900 mg is associated with a modest gain in efficacy, whereas the additional benefit gained by increasing the daily dose from 900 to 1200 mg is small: principally shifting approximately 2.5% of subjects from the 20 to 40% seizure reduction category to the 80 to 100% seizure reduction category. As will be described below, the meager increment in efficacy between the 900 and 1200-mg daily doses is important, because many of the adverse events were dose-related.



Dr. Siddiqui, the statistical reviewer, agreed with the applicant's calculations on the primary and secondary endpoints, as well as with sensitivity analysis that excluded 6 sites considered to have irregularities in trial 205. Dr. Siddiqui also performed additional sensitivity analyses, including ANCOVA analyses on the observed total partial seizure frequency, post-baseline, and ANCOVA analyses on the log-transformed total partial seizure frequency, post-baseline. These analyses were consistent with the principal conclusions of efficacy.

The dropout rates during the double-blind phase in the three trials were relatively high and appeared to be dose-dependent, ranging from 15 to 22%, 25 to 28%, 31 to 34%, and 39% in the placebo, 600, 900, and 1200 mg/day groups in the various trials. The majority of withdrawals were related to adverse events, particularly in higher-dose groups.

In view of the high dropout rates, the statistical reviewer conducted two sensitivity analyses across trials 205, 301, and 302. In the first analysis, seizure data from titration phase were used for patients who dropped out and lacked subsequent data. In the second analysis, subjects who dropped out during the titration phase were assigned non-responder status. The findings were consistent with the protocol-specified analyses.

Subgroup analyses by age and sex found no important differences. Treatment effects in trial 301 were analyzed by region: results at North American sites (US plus Canada) were compared to results at other sites (Mexico and South America). Although an ezogabine treatment effect was apparent in both geographic regions, the treatment effect at North American sites (9%) was far less than at Mexican and South American sites (39%). There were insufficient numbers of non-Caucasians groups to perform any meaningful analysis.

The statistical reviewer concluded that “the findings of the three studies confirmed that ezogabine (600, 900, and 1200 mg/day) is an effective, add-on therapy in the treatment of partial seizures,” and the clinical reviewer and cross-discipline team leader agreed. As noted above, however, there is little gain in efficacy realized by increasing the daily dose from 900 to 1200 mg, a fact that must be weighed against the dose-relatedness of adverse reactions.

**Safety:**

**Exposure**

The safety database in the original submission included 2168 subjects exposed to at least one dose of ezogabine. This number included 1365 subjects with epilepsy in the phase 2 and 3 trials, 669 subjects in clinical pharmacology studies, and 135 subjects with post-herpetic neuralgia or bipolar disorder.

The resubmission included new safety data obtained in the interval from the 120-day safety update of the original NDA submission (October 2, 2009) to the end of the “Final Safety Update” of the resubmission (September 30, 2010). This one-year interval included safety data from 235 subjects from the long-term open-label extension trials of studies 301 and 302, as well as from 108 healthy subjects enrolled in clinical pharmacology studies.

Table 3 summarizes the durations of therapy for the salient dose regimens of ezogabine used in phase 2 and 3 trials of epilepsy:

**Table 3: Duration of ezogabine exposure in phase 2 and 3 epilepsy trials – original submission**

duration	Ezogabine dose		
	≥ 600 mg	≥ 900 mg	≥ 1200 mg
> 3 months	1195	782	227
> 6 months	765	540	156
> 12 months	453	318	100

The exposure exceeds recommendations in the ICH E1 Guideline for drugs intended for long-term treatment of non-life-threatening conditions (>300 subjects for 6 months; >100 subjects for 1 year; >1500 overall).

In phase 2 and 3 trials, mean and median durations of treatment were 303 and 235 days, respectively. Most subjects were Caucasians between the ages of 18 and 64. Both sexes were well-represented. Blacks were underrepresented in the database (only 2.5% of subjects).

### Deaths

Dr. Dinsmore summarized deaths in the ezogabine development program, including the compassionate use program. There were a 17 deaths overall, with 13 occurring during treatment with ezogabine. There were 4 deaths in pre- or post-treatment intervals.

In the controlled treatment phases of epilepsy trials, 2 of 813 (0.2%) ezogabine-treated patients died compared with 3/427 (0.7%) of placebo patients. In the opinion of the review staff, no deaths were directly attributable to ezogabine.

A total of 8 deaths in ezogabine-treated patients met criteria for possible or probable Sudden Unexplained Death in Epilepsy (SUDEP). One death occurred in a morbidly obese 34 year-old female who had advanced coronary artery disease on autopsy. This death was classified as **"SUDEP cannot be excluded."** Depending on the selected cut-off date, the calculated rate of SUDEP in this development program ranged from 4.4 to 5.7 deaths/1000 patient years. As noted by Dr. Dinsmore, the applicant estimated from the literature that the rate of SUDEP ranges from 0.09 deaths/1000 patient-years in studies of patients with newly diagnosed epilepsy to 9.3 deaths/1000 patient years in a study of refractory patients referred to epilepsy surgery centers. Dr. Hershkowitz opined that the rate of SUDEP in the development program seems to be in line with expectations, given that patients who are selected for study are relatively refractory. He added that the rate is similar to those of contemporary epilepsy trials analyzed by the Division. In those trials, rates of SUDEP have ranged from 3.5 to 4.0 events per 1000 patient-years.

### Dropouts and Discontinuations

Overall, subjects who received ezogabine were more than twice as likely to discontinue as subjects who received placebo. In all controlled epilepsy trials, 25% and 11% of subjects in the ezogabine and placebo groups discontinued, respectively. Adverse events were the principal reason for discontinuation, and discontinuations were dose-related, with 17, 25, and 31% of subjects discontinuing in the 600, 900, and 1200 mg/day groups, respectively.

### Safety Concerns of Special Interest

#### Urinary Tract Disorders

As noted above, ezogabine affects potassium channels in urinary bladder muscle, and toxicity was observed in non-clinical studies. In the clinical trials, therefore, urinary tract adverse events were sought as adverse events of interest. In addition, some trials included assessment of the 7-question American Urological Association Symptom Index score and determination of post-void residual bladder volumes by ultrasound.

During the double-blind phase of randomized controlled trials, renal and urinary tract adverse events were reported in greater proportions of subjects who received ezogabine than placebo: 17% versus 13%, respectively; relative risk = 1.3.

Notable urinary tract adverse events in the development program (ezogabine vs. placebo, respectively) were dysuria (2.3% versus 0.7%), hesitation (2.2% versus 0.9%), chromaturia (1.6% versus 0.2%), hematuria (1.6% versus 0.7%) and abnormal urinalysis (1.6% versus 0.9%). Urinary retention was reported in 0.9% and 0.5% of subjects in the ezogabine and placebo groups, respectively. Urinary tract infection was the most common adverse event in this group, but was reported more frequently in patients who received placebo (4.3% vs. 4.7%, for ezogabine and placebo, respectively).

Analyses of the American Urological Association Symptom Index score did not show any clear trends. As Dr. Dinsmore pointed out, this is not unexpected, given that the overwhelming majority of subjects had no urinary tract symptoms at all.

There were 4 serious adverse events in the urinary system in the ezogabine group (renal colic, urinary retention, atonic bladder, and atonic bladder/urinary incontinence) compared to 1 in the placebo group (urinary retention). For the overall phase 2/3 safety database, there were 22 SAEs in 17 ezogabine-treated subjects referable to the urinary system. Urinary retention was the most frequent SAE (n=8). Of note, the median age of these subjects (37) and sex (50% male) match the demographics of the safety database as a whole. Thus, the data do not suggest that particular demographic groups are more vulnerable to urinary retention, a finding that, if present, could have provided a means to mitigate risk.

Six (6) urological adverse events led to drug discontinuation of ezogabine-treated subjects in the controlled trials (urinary tract infection, renal failure, hematuria, atonic bladder, urinary retention, nephritis) compared to 3 in placebo-treated subjects (polyuria, polyuria/urinary retention, and renal colic). In the overall phase 2/3 trial database, there were 17 withdrawals for urinary tract adverse events. One subject developed an obstructive uropathy picture without identifiable obstruction, suggesting drug-induced alteration in bladder function.

A striking finding, as Dr. Dinsmore notes, is that 25% of patients treated with ezogabine in phase 2/3 epilepsy trials reported at least one urological adverse event. Urinary tract infection (7.7%) was the most commonly reported urological adverse event, followed in decreasing frequency by hesitation (3.1%), abnormal urinalysis (2.6%), dysuria (2.4%), urinary retention (1.9%), hematuria (1.8%), chromaturia (1.7%), polyuria (1.6%), and residual urine volume present (1.1%). It is also noteworthy that these adverse events occurred despite heightened monitoring and awareness in a clinical trial environment.

There was no relationship between baseline post-voiding residual (PVR) or change in PVR and the likelihood of developing urinary retention. Sex was not a risk factor. Age was generally not a risk factor, although subjects over the age of 50 appeared to be at slightly greater risk. At the advisory committee meeting, there was some concern regarding the apparent lack of understanding of the mechanism(s) underlying the urinary adverse events, and some committee members suggested post-marketing urodynamic studies to provide mechanistic insight.

Dr. Dinsmore assessed the timing of the 25 cases of urinary retention identified in the safety database, finding that 18% of cases occurred within the first month, and 59% occurred within the first six months; however, cases were observed as late as 2.5 years after initiation of ezogabine. His analyses did not identify an obvious relationship to dose, with events occurring at doses as low as 300 mg/day. Conversely, analyses by Dr Kim, a consultant from the Division of Reproductive and Urological Products, suggested a dose-response.

Dr Kim noted that ezogabine is crystallogenic: nearly 40% of ezogabine is excreted unchanged in the urine, and the drug is insoluble at physiologic urinary pH. Urinary crystals and "amorphous material" were found more frequently in ezogabine-treated patients, and analyses using mass spectrometry identified peaks corresponding to the known molecular weight of ezogabine and its

dimers. Although there was a trend towards more frequent stone formation in subjects on ezogabine than on placebo, no stone was identified as being composed of drug. The consultant opined that ezogabine crystalluria poses a theoretical risk of renal injury secondary to intratubular precipitation and urolithiasis, but noted that such findings were not reported in the phase 3 trials, and the data do not provide a clear signal for ezogabine stone formation.

### Psychiatric and Cognitive Symptoms

Dr. Dinsmore analyzed psychiatric and cognitive symptoms in the randomized controlled trials using a range of preferred terms (e.g., "anxiety," "disorientation," "hallucination," "psychosis," "depression," "abnormal behavior," "euphoric mood," etc.). There was no apparent difference in the overall frequency of these events between the two lower doses of ezogabine (5.7 and 7.0% in the ezogabine 600 and 900 mg/day groups, respectively) and placebo (6.3%). For subjects in the 1200 mg/day ezogabine group, however, the frequency was 16.6%. Psychiatric adverse events led to 28 withdraws in 813 patients in ezogabine-treated subjects (3.4%), versus 8 withdraws in 427 patients (1.9%) in the placebo group.

**With a more focused search on psychotic symptoms ("hallucination," "psychotic disorder," and "psychosis"), however, there was a clear dose-relationship with 0.5, 1.4, 1.8, and 5.0% of patients experiencing these symptoms in the placebo and ezogabine 600, 900, and 1200 mg/day groups, respectively. The applicant's findings were similar, although their numbers were slightly higher: they found events related to hallucination or psychosis in <1, 2, 3, and 7% of patients in the placebo and ezogabine 600, 900, and 1200 mg/day groups, respectively.**

The applicant also noted that these adverse events appeared within the first 8 weeks of treatment in all dose-groups, with most reported within 4 to 8 weeks. When examined by study phase, over half the events were reported during titration (19/32), and the actual dose at the time of symptom onset was generally <1200 mg/day.

**Consistent with the applicant's conclusions, Dr. Dinsmore pointed out that one of the phase 2 studies, study 209, included a rapid up-titration of ezogabine dose, and there was striking incidence of psychotic symptoms, with 5 of 27 subjects discontinuing because of psychotic-like behaviors. Thus, the rate of up-titration appears to be an important factor in the induction of psychotic symptoms.**

One healthy volunteer experienced brief but severe psychosis in a phase 1 study, and 8 subjects in clinical pharmacology studies reported hallucinations as adverse events (the latter adverse events **were reported in the in the applicant's resubmission to our Complete Response**). **Importantly, Dr. Dinsmore notes that the occurrence of psychotic symptoms in healthy subjects participating in clinical pharmacology studies strongly suggests that ezogabine may produce these CNS effects independent of a background CNS disorder and independent of concomitant medications. Clearly, ezogabine-induced psychosis is not simply a postictal or interictal phenomenon.**

Thus, neuropsychiatric symptoms constitute a significant untoward effect of ezogabine, and they are discussed in the Warnings and Precautions section of labeling. They are also discussed in the **Medication Guide, as knowledge of the potential for such symptoms could impact patients'** decisions to start the drug, and such knowledge would also be important for patients who take the drug.

No cases of suicide were reported in the development program. One case of attempted suicide and one case of suicidal ideation were observed in the drug group in the controlled trials, compared to 2 cases of suicidal ideation in the placebo group. Clearly these data are not adequate to permit a robust determination of risk. Ezogabine will receive the FDA class labeling **based on results of the Division's meta-analysis of controlled studies of other AEDs.**

## Cardiovascular Effects

Dizziness was the most common adverse event reported in the pivotal controlled trials, reported in 23% of all ezogabine-treated subjects versus 9% of placebo. One of the potassium channels opened by ezogabine is present in vascular smooth muscle, such that there is a theoretical potential for blood pressure-lowering effects that could lead to dizziness. An outlier analysis performed by Dr. Dinsmore, however, did not support the concept that dizziness was blood pressure-related. Specifically, decreases of 20 mmHg in standing systolic blood pressure over baseline were observed in similar fractions of subjects in all treatment groups: 22, 25, 21, and 24% of subjects receiving placebo, ezogabine 600, 900, and 1200 mg/day, respectively. It is not clear if subjects who reported dizziness were concordant with subjects who had decreases in blood pressure.

Two notable cardiac arrhythmias were observed in non-epilepsy studies in subjects exposed to high doses of ezogabine. The subjects had histories of drug abuse but were otherwise healthy: 1) A 34 year-old woman with a history of bradycardia experienced asystole for 25 seconds with syncope, 1.8 hours after receiving a single 900-mg dose of ezogabine. Electrolytes were normal; a subsequent stress echo was negative. 2) A 41 year-old male had 4 runs of non-sustained ventricular tachycardia, as long as 9 beats in length.

The review team noted that these isolated cases make it difficult to attribute causality to the drug; in particular, the review team thought that having a history of bradycardia confounds the episode of asystole. I disagree with that logic, however. Bradycardia is common in younger women; true asystole is not. The episode corresponded fairly well in time with  $T_{max}$ , and it is difficult to find other reasons why the subject would have had asystole at that point in time. (Apparently, this was not a vasovagal episode associated with phlebotomy.) In other words, the event incriminates the drug beyond a reasonable doubt. The important point is that the event occurred after a 900-mg dose, whereas the highest dose recommended in labeling will be 400 mg, given TID. This case will be described in the overdose section of the label. The episodes of non-sustained ventricular tachycardia in the 41 year-old male are not particularly troubling in my opinion, as this arrhythmia is commonly observed in asymptomatic individuals without known cardiovascular disease.

During the review process, the review team expressed considerable consternation regarding cases of atrial fibrillation reported in a randomized, placebo-controlled study of ezogabine in post-herpetic neuralgia. There were 4 cases of atrial fibrillation in 125 subjects randomized to ezogabine (3.2%), versus no cases in 62 subjects in the placebo group. Careful review of the cases showed that each subject had risk factors for atrial fibrillation, and given that the subject population was generally elderly (mean age 63), atrial fibrillation is actually expected. In any case, with the small number of events (and the 2:1 randomization), it would be difficult to conclude that the imbalance is **anything more than a chance finding**. As noted above, however, the drug's mechanism of action involves potassium channels, and adverse events associated with high doses of the drug, although unexpected, could be drug-related. Certainly the case of asystole, described above, is drug-related.

The applicant performed a thorough QT study in 120 healthy subjects. The highest dose examined was 400 mg TID, because higher doses were not thought to be tolerable; in fact, only 26 of 38 subjects tolerated the target dose. The mean difference in QTcF (Fridericia correction) between ezogabine 400 mg TID and placebo (placebo-subtracted change from baseline,  $\Delta\Delta QTcF$ ), was 7.7 msec, and the upper bound of the 90% CI was 11.9 msec, observed 3 hours after dosing. The largest lower bound of the two-sided 90% CI for the  $\Delta\Delta QTcF$  for moxifloxacin was greater than 5 ms. The Interdisciplinary Review Team for QT Studies noted that the study suffered from several

problems (i.e., the rising phase of the moxifloxacin arm was not adequately evaluated, and supratherapeutic concentrations of ezogabine were not studied because of tolerance issues).

Electrocardiograms were performed during the controlled epilepsy studies, but the results of the analyses revealed inconsistent findings.

The greatest differences from placebo in QT interval (msec) were observed at Weeks 12 and 18, in an inconsistent pattern:

	Placebo (n=427)	600 mg/d (n=281)	900 mg/d (n=273)	1200 mg/d (n=259)
Week 12	1.4	2.1	16.7	14.8
Week 18	3.6	11.3	10.6	3.3

An outlier analysis of the percentage of subjects with changes in QTcF interval from baseline:

	Placebo (n=403)	600 mg/d (n=266)	900 mg/d (n=255)	1200 mg/d (n=232)
> 30 msec	8%	10%	12%	12%
>30 and ≤60 msec	8%	10%	11%	12%

There were no meaningful changes between placebo and any ezogabine dose in PR interval, QRS interval, or heart rate. There were no differences in the percentage of patients with QT intervals of >450 msec between the placebo and ezogabine groups (approximately 1% in each group).

The QT Interdisciplinary Review Team suggested that the label include a general statement to the effect that the **“QT interval should be monitored when POTIGA is prescribed with medicines known to increase QT interval and in patients with congenital long QT syndrome, heart failure, ventricular hypertrophy, hypokalemia, or hypomagnesemia,” and such language will be included in labeling.**

#### Hepatic and Biliary Effects

It was hypothesized that ezogabine’s potassium channel effects could affect gallbladder smooth muscle in the same manner as it affects urinary bladder smooth muscle, and in dogs, ezogabine was found to cause pathologic changes in the liver adjacent to the gallbladder, thought to be related to this mechanism.

In the ezogabine clinical development program, however, the numbers of adverse events referable to gallbladder were small, and were similar in the ezogabine and placebo groups.

In the epilepsy controlled trials, liver function test (LFT) elevations reported as an adverse event were slightly more frequent in subjects who received ezogabine (3.1%) than placebo (1.4%).

The percentages of patients with LFTs > 3 X upper limit of normal (ULN) were 1%, 1.5%, 3.1%, and <1% in the placebo, 600, 900, and 1200 mg/day ezogabine groups, respectively. There were no differences in the percentage of patients with LFTs between 5 and 10X ULN. There were no Hy’s law cases.

As noted by Dr. Dinsmore, however, 27 ezogabine-treated subjects discontinued treatment secondary to LFT abnormalities: 13 were in controlled trials, including 7 in epilepsy trials (7/813; 0.9%). One had an alanine aminotransferase (ALT) of 10X ULN and a direct bilirubin of 2.4, a case that remains under consideration at the time of writing of this memorandum. Three (3) other subjects had ALT elevations greater than 10X ULN, without other laboratory abnormalities. In 23 of 27 subjects, the abnormalities resolved upon discontinuation of treatment (in the other 4 patients, the data are not available).

Central analysis showed small increases in ALT and aspartate aminotransferase (AST) that were not dose-dependent. There was a consistent increase in bilirubin that the applicant attributed to interference of ezogabine and its NAMR metabolite with the analytic method used to measure bilirubin. Interference with the bilirubin assay is to be noted in the label.

#### Blood Dyscrasias

Neutropenia was identified as a potential safety signal in a canine toxicity study where NAMR was administered, prompting evaluation of neutropenia and infections in the ezogabine clinical program. **No clear signal emerged. The applicant generated a query of "neutropenia or infection-related adverse events," and found a similar frequency between the placebo and ezogabine groups (approximately 7%).** Whereas leukopenia was reported at a higher frequency in ezogabine-treated subjects than placebo subjects (1.2% versus 0.5%), the opposite was true for neutropenia (0.2% versus 1.2%). Also, there was 1 case of pancytopenia reported in the placebo group, and none in the ezogabine group. Taken together, there does not appear to be a clear trend for neutropenia.

#### Abuse Potential

The Controlled Substance Staff concluded that ezogabine is a central nervous system depressant with an abuse potential similar to drugs in Schedule (b) (4) of the Controlled Substances Act (CSA). They recommended that ezogabine be placed in Schedule (b) (4) of the CSA, a conclusion with which the applicant agreed. At the time of this writing, however, final scheduling of this product under the CSA has not been completed by the Drug Enforcement Administration (DEA). (b) (4)

#### Risk Evaluation and Mitigation Strategy (REMS):

The REMS consists of a communication plan and a timetable for submission of assessments of the REMS. Independent of the REMS, there is a Medication Guide highlighting the risks of urological problems, psychiatric problems, and suicide. The Division of Risk Management is in agreement with the applicant's final REMS proposal.

#### Risk Assessment of Established and Proprietary Names:

The Division of Medication Error Prevention and Analysis (DMEPA) identified a concern with the originally proposed established name, (b) (4) because of orthographic and phonetic similarities and potential name confusion with (b) (4) (the established name for (b) (4)). The

Division agreed with DMEPA's concern, and suggested that the applicant petition the United States Adopted Names (USAN) Council for a new established name. The applicant pursued two alternative names; the established name (b) (4) was eventually rescinded in favor of a new USAN-designated established name: "ezogabine."

Because DMEPA does not have authority over established names, they do not typically comment on a negative finding regarding their potential to function as a source of medication error. In this case, however, because the originally proposed established name was changed in light of a safety concern, DMEPA commented for the administrative record. They found no overt risks with the new established name "ezogabine."

DMEPA had no objection to the proprietary name "Potiga" after a careful review.

#### Advisory Committee:

Primarily because of Potiga's capacity to cause urinary retention, the application was referred to a meeting of the Peripheral and Central Nervous Systems Advisory Committee on August 11, 2010. The standing committee was supplemented with experts in epilepsy and urology.

The committee voted unanimously that the applicant had provided substantial evidence of effectiveness for ezogabine as adjunctive treatment for adults with partial seizures. By a vote of 11 "yes," 0 "no," and 2 abstentions, the committee voted that the risk of urinary retention could be mitigated by appropriate patient monitoring, and that, in general, adequate monitoring could consist of patient education and routine clinical vigilance. They opined that for the typical patient, sophisticated urologic monitoring was unnecessary, and that specific monitoring for urinary stones or infections was not required.

They did offer the view that for patients who could not reliably report symptoms of urinary retention (for example, patients with cognitive impairment), urologic consultation could be helpful.

The committee also recommended that the applicant perform, in phase 4, urodynamic studies to try to identify the mechanism of urinary retention, and that patients under the age of 12 should not be treated with ezogabine until these studies are performed. They agreed that there were no other safety issues that would preclude approval.

#### Postmarketing Requirements:

The clinical review team recommends post-marketing requirements for a urodynamic study and for a prospective cohort study of patients starting on ezogabine as compared to those starting on other AEDs.

The clinical pharmacology review staff recommends post-marketing requirements for an *in vitro* study to evaluate ezogabine's potential to inhibit CYP2B6, an *in vitro* study to evaluate whether ezogabine is a substrate for major transporters in the kidney, and a clinical trial to evaluate the acetyl metabolite of ezogabine (NAMR) as an inhibitor of P-glycoprotein using digoxin as a probe substrate.

The controlled substances staff requested a post-marketing non-clinical (animal) study to better characterize whether or not ezogabine can produce physical dependence. The applicant did not perform adequate studies in humans to address this issue.

The applicant has agreed to complete the aforementioned studies, as well as deferred pediatric studies required under section 505B(a) of the FDCA.

## Conclusions:

The applicant submitted three randomized, double-blind, placebo-controlled trials that provide evidence of effectiveness for ezogabine for the proposed indication: adjunctive therapy for the treatment of adults with partial-onset seizures. The effect size was comparable to that shown for newer AEDs. The results were, for the most part, statistically persuasive and robust to exploration (the exception was the 600-mg daily dose in trial 205, where there was a trend favoring efficacy, but the results were not statistically significant).

A key question regarding efficacy is the extent to which the highest daily dose studied (1200-mg) should be encouraged or discouraged in labeling. One trial (205) compared the 900- and 1200-mg doses directly, and found only a minimal difference on the primary outcome measure. Examination of the histogram shown in the figure above, as well as a cumulative distribution function for percent reduction in 28-day seizure frequency provided by the applicant, suggest that little efficacy is gained by increasing the daily dose from 900 to 1200 mg. Conversely, adverse events are clearly more frequent at the higher dose.

The review team thought there was a reasonable case for including the 1200-mg daily dose in labeling, despite the minimal gain in efficacy, and I agree with their view. My logic is that 1) seizures are medically important events; 2) patients should be able to develop some sense of whether or not they derive greater seizure control from the higher dose; 3) patients will be cognizant of the side effects; and 4) those side effects are, by-and-large, reversible. In other words, patients should recognize if they are deriving benefit and recognize if they are harmed, and harm should be reversible. The possible exception here is urinary retention, which occurred in the clinical trials **despite considerable attention directed towards its detection**. In "real world" use, urinary retention, and more importantly, renal damage, could pose greater risks. The applicant proposed to manage this risk with monitoring, appropriate product labeling, and by providing a Medication Guide to patients. This approach seems rational, and the planned prospective cohort study could help resolve the magnitude of risk.

Ezogabine plainly causes significant dose-related neuropsychiatric adverse events, which (fortunately) resolve upon discontinuation. These symptoms will be prominently described in labeling, and are included in the Medication Guide.

The Division was particularly concerned about the risk of arrhythmias, particularly atrial fibrillation. As noted above, atrial fibrillation was reported in a study of ezogabine for post-herpetic neuralgia, in a patient population of relatively advanced age (mean age 63 years). There were 4 cases of atrial fibrillation in 125 subjects randomized to ezogabine (3.2%), versus none in 62 subjects in the placebo group. Given that the number of cases is small, that randomization was 2:1, and that atrial fibrillation is relatively common in this older patient population, much of the concern seems unwarranted. Had there been a single case of atrial fibrillation in the placebo group, there would have been no concern here at all. Conversely, the single case of asystole in a young volunteer who received a single dose of 900 mg ezogabine seems important to highlight in labeling, as noted above. Ezogabine appears to produce a slight increase in QT, an effect that should be adequately managed in labeling.

Ezogabine produced considerable increases in hepatic transaminases. Although a few patients experienced mild elevations in total bilirubin, **there were no Hy's law cases**. All transaminase elevations resolved after discontinuation of ezogabine, and its capacity to increase transaminases can be managed through labeling.

Given that the applicant has adequately addressed the issues responsible for the original complete response action, and for all of the reasons outlined above, I am today approving this NDA.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ELLIS F UNGER  
06/10/2011