CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022345Orig1s000

SUMMARY REVIEW

MEMORANDUM

DATE: June 9, 2011

FROM: Russell Katz, M.D.
Director
Division of Neurology Products/HFD-120

TO: File, NDA 22-345

SUBJECT: Recommendation for action on NDA 22-345, for the use of Potiga (ezogabine) as adjunctive treatment of partial seizures in adults

NDA 22-345, for the use of Potiga (ezogabine) as adjunctive treatment of partial seizures in adults, was submitted by Valeant Pharmaceuticals North America, on 10/30/09. The application contained information on the following tablet strengths: 50, (b) (4) 200, 300, and 400 mg. According to the sponsor, ezogabine stabilizes neuronal KCNQ channels in the open position, and is presumably the first potassium channel opener developed for the treatment of epilepsy. The application contains the results of three randomized, placebo controlled trials, as well as the requisite safety data. The Agency issued a Complete Response to the sponsor on 11/30/10; the primary reason for the CR action was stated as follows, taken verbatim from the CR letter:

NONCLINICAL

The NDA is not approvable due to the high specification limit proposed for the mutagenic impurity (b) (4) *was reproducibly positive in the Ames assay, both in the presence and absence of metabolic activation. Although* (b) (4) *was negative when tested in vivo in a combined rat micronucleus and Comet assay, we believe these results do not provide a basis for dismissing the mutagenic potential clearly demonstrated in the Ames assay. The Ames assay and the in vivo assays evaluate different genotoxicity endpoints that do not always correlate and, at this time, there are inadequate data to determine whether a negative Comet assay has adequate negative predictive value to provide reassurance in the face of a positive Ames test. An earlier effort to establish a higher Threshold of Toxicological Concern for* (b) (4) *based on an assessment of the structure-activity relationship (i.e.,* (b) (4) *) was considered inadequate, because it relied on several unsubstantiated assumptions, in particular, that published carcinogenicity data on structurally related compounds accurately reflect the carcinogenic potential of* (b) (4) *and that doses of structurally related compounds can be extrapolated to* (b) (4) *. Therefore, you will need to lower the specification limit to one that results in a daily dose of*

(b) (4) *considered acceptable for a genotoxic impurity (for ezogabine at proposed doses,* (b) (4) *).*

Another, less important deficiency noted in the CR letter was as follows:

BIOPHARMACEUTICS

(b) (4)

Noted during the initial review cycle was ezogabine's potential to cause urinary symptoms, including cases of urinary retention. This action is presumably related to the pharmacology of ezogabine, and was fully discussed at a meeting of the Peripheral and Central Nervous Systems (PCNS) Advisory Committee held on 8/11/10.

The sponsor responded to the CR letter with a submission dated 4/15/11. The submission contains additional chemistry and manufacturing (CMC) information, and additional clinical information. The CR has been reviewed by Dr. Mohan Sapru, CMC, Dr. Ta-Chen Wu, Office of Clinical Pharmacology, Drs. Lori Love and Katherine Bonson, Controlled Substance Staff (CSS), Dr. Steven Dinsmore, medical reviewer, and Dr. Norman Hershkowitz, neurology team leader and Cross Discipline Team Leader (CDTL).

Briefly, as Dr. Sapru describes, the sponsor has modified the manufacture of the drug substance so as to limit the amount of the (b) (4) impurity to (b) (4) at the maximum recommended dose of (b) (4); this limit is below the maximum daily allowance of 1.5 mcg/day for a genotoxic impurity. (b) (4)

Dr. Dinsmore notes that the sponsor has provided safety data on an additional 313 patients enrolled in open-label extensions from the time of the cut-off for the initial 120 day safety update (10/2/09) to the new cut-off date (9/30/10), as well as for 65 healthy subjects enrolled in clinical pharmacology studies.

There were a total of 2 additional deaths in the open-label experience, one in a patient with a sub-dural hematoma and one patient was found dead; in this latter case, there was a question of non-compliance. A total of 13 serious adverse events were noted in patients, and 3 in healthy subjects in clinical pharmacology

studies. No new adverse events not previously seen were noted in the additional experience. Of note, 3 additional cases of urinary retention were noted; these occurred at 761, 845, and 889 days after the initiation of treatment; one was in a 20 year old man and one was in a 26 year old woman. None of these cases were considered serious, nor did any result in treatment discontinuation, but one case is of note.

A 20 year old man experienced urinary retention on Day 845 of treatment and was catheterized. On day (b) (6), he was admitted to the hospital for splenic hemorrhage; he was discharged on Day (b) (6), at which time the catheter was removed.

A recommendation for placement in Schedule (b) (4) of the Controlled Substances Act has been made by the CSS. At the time of this writing, a final determination of scheduling has not been made (the issue is being reviewed at the Drug Enforcement Agency at this time).

Several of the review teams have proposed the following Post Marketing Requirements (PMRs) be conducted by the sponsor; these have all been discussed with the sponsor, and they have agreed to submit protocols, perform the studies, and submit the study reports by the appropriate dates:

1 Conduct a prospective, randomized, placebo-control, double-blinded efficacy/safety trial in children ≥12 years old.

2 Conduct a long-term open label extension study of ezogabine in children ≥12 years old.

3 A prospective cohort study to better define the risk of urinary retention in patients with epilepsy treated with ezogabine and how the risk may vary with demographics (e.g. age), comorbidities that influence voiding (e.g. BPH, Multiple Sclerosis) and concomitant medications that may influence voiding. The study will be performed utilizing a research database to compare patients started in two cohorts, those started on ezogabine with those started on other anticonvulsants, for the incidence of urinary retention. The study will analyze approximately 2,000 to 4,000 Ezogabine exposed patients.

4 An *in vitro* study to evaluate whether ezogabine is a substrate for major transporters in the kidney

5 An *in vitro* study to evaluate to evaluate the potential for ezogabine to inhibit CYP2B6.

6 An animal physical dependence study to evaluate whether chronic administration of ezogabine produces a withdrawal syndrome following drug discontinuation.

7 A controlled urodynamic trial in patients with epilepsy. The trial should include patients of different ages and in both sexes. Pre- and post- drug urodynamic measures should be carefully collected. Urodynamic measurements should include, although not necessarily be limited to, uroflowmetry, multichannel cystometry, electromyography (EMG), and subjective sensory reporting.

8. A clinical trial to evaluate the acetyl metabolite of ezogabine (NAMR) as an inhibitor of P-glycoprotein using digoxin as a probe substrate.

Given that the sponsor has adequately addressed the reasons for the CR action, and given that they have agreed to perform the PMRs described above, we recommend that the application be approved with the attached product labeling (including Medication Guide), to which we and the sponsor have agreed. In addition, a Risk Evaluation and Mitigation Strategy (REMS) will be required. The REMS will consist of a communication plan that itself consists of Dear Health Care Practitioner letters describing the risk of urinary retention.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUSSELL G KATZ
06/10/2011