CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	6/8/11
From	Norman Hershkowitz, MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	22345
Applicant	Valeant Pharmaceuticals
Date of Submission	4/15/11
PDUFA Goal Date	6/15/11
	Response to CR letter
Proprietary Name / Established (USAN) names	Potiga/ezogabine
Dosage forms / Strength	50 mg, 200 mg, 300 mg and 400 mg strength tablets
Proposed Indication(s)	Adjunctive treatment of partial onset seizures in adults.
Recommended:	Approval

1. Background

Ezogabine is a new molecular entity that was previously submitted for approval on 10/30/09. At that t it was determined that there was adequate clinical evidence for efficacy and safety to permit approval. However, one chemistry/carcingencity impurity matter resulted in the issuing of a CR letter on 11/30/10. Genetic testing of the batches of the drug indicated it to be potentially mutagenic, based upon a positive Ames test. This was thought, at least in part, to be potentially caused by the presence (b) (4) a mutagenic impurity, which far exceeded the regulatory limits. Although the Sponsor was willing to reduce this impurity from (b) (4) the division decided that this would not be sufficient as it was believed that this impurity can be reduced further and that Potiga, at face, did not appear to present any clinical or safety advantage to the numerous drugs that were already labeled for partial seizures. A reduction to at least (b) (4) was requested.

2. CMC/Device

As per the chemistry reviewer, Dr. Mohan K. Sapru, the Sponsor has altered the manufacturing process, which lowered the concentration of (b) (4) impurity to an acceptable concentration of (b) (4). They now recommend approval.

The original NDA submission included a request for approval of 50, (b) (4) 200, 300 and 400 mg strength tablets. The CR letter expressed concern regarding the observation that (b) (4)

(b) (4)

3. Nonclinical Pharmacology/Toxicology

4. Clinical Pharmacology/Biopharmaceutics

Dr. Ta-Chen Wu reviewed additional Clinical Pharmacology information provided by the Sponsor. This additional information included an *in vitro* study that showed that that the N-acetyl metabolite of ezogabine (NAMR) inhibited P-glycoprotein–mediated transport of digoxin in a concentration dependent manner suggesting that NAMR may inhibit renal clearance of digoxin.

To clarify this issue the Clinical Pharmacology reviewer is recommending an additional PMR that consists of a study in humans that evaluates NAMR as an inhibitor for P-glycoprotein (P-gp) using digoxin as a probe substrate.

5. Clinical Microbiology

Not Applicable

6. Clinical/Statistical- Efficacy

See prior CDTL review.

7. Safety

Dr. Dinsmore performed a review on the safety update. The safety update included data from 313 epilepsy patients participating in long term open label extension trials and 65 healthy subjects in multiple dose clinical pharmacology studies. Pateints in Clinical Pharmacology trial were also used to examine ezogabine's effect on gallbladder volume.

A review of the general safety information failed to indicate any new safety issue above and beyond those already described in the first review and included in the label.

The Sponsor, as noted above, performed a study to examine gall bladder volume. *In vitro* animal data studies suggested the potential for ezogabine to relax the gall bladder as it does the urinary bladder. Moreover, *in vivo* dog studies, but not other animals, suggested the possibility of cholestasis. The Sponsor examined the effect of ezogabine on gallbladder volume with exposures within therapeutic ranges and over a period of weeks. Their analysis concluded, no effect. Dr. Dinsmore attempted to examine cumulative dose response curves from this data to determine if he could identify an effect. He also concluded no obvious effect although he notes that 2 patients (r of 0.7 and 0.6) out of the 32 examined exhibited a potentially significant positive dose response relation. Others, however (information not noted in his review) exhibited significant negative slopes. In fact the total number of negative slopes mirrored or exceeded that of the positive slopes. Dr Dinsmore performed a reexamination of the complete database, including that from the original NDA and present safety update, and could not find no correlation between treatment and cholestasis based upon adverse event reporting. Indeed the adverse event of cholecystitis was much more common in the placebo (0.7 %) then in the drug group (0.1 %). Dr Dinsmore concludes, "ezogabine may have an influence on gall bladder contractility but there is currently insufficient evidence to change labeling. Focused pharmacovigilance is appropriate and is currently planned by the sponsor." This is already in the Sponsor's risk management program and is part of our prior pharmacovigilance recommendation.

8. Advisory Committee Meeting

See prior CDTL review.

9. Pediatrics

See prior CDTL review.

10. Other Relevant Regulatory Issues

See prior CDTL review.

11. Labeling

See prior CDTL review and labeling.

12. Recommendations/Risk Benefit Assessment

See prior CDTL review. However an additional PMR has been added to PMR to study evaluate the potential of NAMR as an inhibitor for P-glycoprotein (P-gp) using digoxin as a probe substrate.

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/s/

NORMAN HERSHKOWITZ
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