

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205122Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	
From	Norman Hershkowitz, MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	205122/000
Supplement#	
Applicant	Upsher-Smith Laboratories (USL)
Date of Submission	2/11/13
PDUFA Goal Date	With 3 month extension: 3/11/2014
Proprietary Name / Established (USAN) names	Qudexy XR / Topiramate XR
Dosage forms / Strength	Oral Capsules/25 mg, 50 mg, 100 mg, 150 mg, and 200 mg
Proposed Indication(s)	<ol style="list-style-type: none"> 1. Partial Onset Seizures: <ul style="list-style-type: none"> • Adjunctive Tx: 2 years to adults • Monotherapy Tx: 10 years to adults 2. Primary Generalized Tonic-Clonic Seizures: <ul style="list-style-type: none"> • Adjunctive Tx: 2 years to adults • Monotherapy Tx: 10 years to adults 3. Adjunctive Tx for seizures associated with Lennox-Gastaut, 2 years to adults
Recommended:	Approval

1. Introduction

Qudexy XR is an extended release formulation of the referenced label drug (RLD) Topamax (topiramate) (NDA 020505). Topamax is labeled for twice daily use, while Qudexy XR is labeled for daily use. Topamax was originally approved in 1996 with later efficacy supplements submitted for different indications and populations. Presently Topamax is approved for monotherapy and adjunctive therapy for seizures classified as partial onset seizures (POS) and primary generalized tonic-clonic seizures (PGTCS) in patients older 2 years and above as well as adjunctive treatment in patients with seizures associate with Lennox-Gastaut syndrome (LGS) in patients 2 years and above. It is also indicated as migraine prophylaxis in adults. The Sponsor is asking for these same seizure indications for Qudexy XR, with the exception that they are asking that it only be labeled for monotherapy use in POS and PGTCS in patients 10 years of age and older; the exclusivity of these indications is still protected.

2. Background

The Division met with the Sponsor on 5/20/08 to discuss what type a study would be required to gain approval of an extended release formulation of topiramate, considering that the IR formulation is already approved. The Sponsor was provided with the following advice (transcribed from the meeting minutes), which essentially describes the division's policy on such issues:

- “1. Multiple dose bioequivalence studies should be performed for comparison to the commercially available IR formulation. In these studies comparison for bioequivalence should not only include Cmax and AUC, but Cmin as well.
2. The different shape of the PK curves between ER and IR formulations could result in different pharmacodynamic properties. The division is concerned that the therapeutic effect may be dependent on the rate of change in concentrations. You should present an argument based on an understanding of the PK-PD relationship of the drug that would justify approval based on pharmacokinetic equivalence. Absent a compelling argument, an additional clinical efficacy study may be needed.”

Following this meeting, another Sponsor (Supernus) was provided with similar advice for another formulation extended formulation for topiramate (Trokendi). However, in that case the Sponsor provided the division with an analysis plan that provided an argument that the shape of the curves was minimally different between the RLD Topamax and their experimental formulation. It was determined that such an analysis should be considered as proprietary. USL subsequently carried out a phase 3 controlled clinical trial.

On 11/30/12 the Division had a Type A meeting, where the Sponsor raised the issue as to whether there may be another way to obtain approval based upon PK data. The Sponsor presented a PK study that compared partial AUCs study, which is similar to that presented by Supernus. The Division believed that the Sponsor's proposed PK study could alone support approval and the application would be fileable, but recommended further PK analysis. On 2/11/13, the Sponsor subsequently submitted a 505(b)(2) application that depended on the PK study for approval. Based upon a prior email communication from the Sponsor (3/15/13), the Division was aware that the Sponsor was intending on providing additional information from the ongoing phase 3 controlled clinical trial after the NDA was filed. Because there was adequate information for review of the NDA without the phase 3 study data, the Division recommended that the Sponsor only submit “top line” efficacy results along with the safety results that they were intending to submit from the phase 3 controlled clinical trial. This was requested on April 26, 2013 in the 74 day letter. This request was to obviate the need for a more thorough review that may extend the review clock¹. Of course, at this time it was not

¹ It is noteworthy that during the October 31, 2012, Type A meeting with USL, USL discussed the submission options available to achieve the earliest approval possible. USL asked if a complete submission based on PK in the first quarter of the year could be followed in the second quarter by clinical trial data. The Division stated this was an unsatisfactory proposal because a clinical trial would not be a minor amendment. The Division noted that submission of a clinical trial would extend the review clock an additional three months, so unless the amendment

determined that such information provided justification for approval, only that the argument appeared reasonable and, as a result, the application was fillable. While the application was under consideration, the Sponsor submitted, along with their 120 day safety update (5/21/13), a full study report of the phase 3 controlled clinical trial, including a detailed safety and efficacy analysis and new labeling changes based upon this information. Because of the extensive nature of this submission, this was considered a major amendment and the the application due date was extended. Based upon the Project Manager's, Dr. Holmes, notes, the final decision that the PK study alone was sufficient to support approval was communicated by the PK team on 12/11/13, at a team meeting. The Division concludes that the phase 3 study data were supportive, but not essential, to the approval of the NDA.

3. CMC/Device

Dr. C. Jewell performed the primary chemistry review. Dr. S. Suarez performed the ONDQA review.

The drug product consists of a topiramate extended release formulation, in the form of capsules containing extended release beads. Chemistry found no quality deficiencies and recommended approval for all dosages. ONDQA concurred with the approval for all dosages and with the extended release designation. The ONDQA reviewer did note that *in vitro* studies suggested that the functional coating leads to rapid *in vitro* drug release from the beads in the presence of 40% ethanol and to a lesser extent in the presence of 20% ethanol. Discussions between the review group, including OCP and Clinical, believed that this should not adversely affect the products bioavailability under normal circumstances of alcoholic "recreational" use (see below).

The Office of Compliance has determined that the manufacturing and testing facilities acceptable.

4. Nonclinical Pharmacology/Toxicology

Not applicable. For toxicological issues of the drug substance the reader is referred to the review of the original reference labeled drug. The new formulation does not present any unique toxicological issues.

5. Clinical Pharmacology/Biopharmaceutics

Dr. Wu Performed the OCP review. Dr. Men was the OCP Team Leader.

(received May 21, 2013) was submitted soon after the PK package (received February 11, 2013) this method would not advance the approval date.

Bioequivalence Evaluation

It has been the Division's policy that because of the potential differences in the shape of the absorption curves between an IR and XR formulations that routine bioequivalent standard comparison (C_{max} and AUC₀₋₂₄) cannot be used to justify equivalency of therapeutic effects of these agents. A new standard, however, was established with the approval of Trokendi XR that examines bioequivalence measures along multiple time points, not just the C_{max} and AUC₀₋₂₄. The basic presumption here is that using this comparison permits the conclusion, that the shape of the absorption curves for both an XR and an IR formulation are essentially the same. This was accomplished by the demonstration of bioequivalence between the IR RLD and the test XR formulation at many multiple time points. Dr. Wu notes that this comparison was accomplished through study P09-003, which he describes as the pivotal bioequivalence study. This study was a randomized, single-center, open-label, 2-way crossover study in 38 healthy subjects (1:1 ratio) that compared the bioavailability of a 200 mg dose of Qudexy XR product administered daily with a 100 mg of the IR RLD administered twice daily (12 hours apart) at steady state. Patients were administered the RLD or Qudexy XR for 14 days and immediately switched to the alternative treatment on day 15; they subsequently received an additional 14 days of the alternative crossover treatment. Dr. Wu notes that a second multiple-dose study, conducted in healthy subjects (P255-103), provided additional supportive evidence. Study P255-103 was a randomized, double-blind, two-period, crossover study in 48 health patients that was principally designed to compare neuropsychiatric factors between both formulation at a variety of doses accomplished through sequential increase in doses to steady state. There was a 21 day washout between periods. The pharmacokinetic information of the 200 mg dose at steady state was leveraged for their additional bioequivalence information.

The Initial analysis of these studies include a comparison of point-to-point BE analysis for partial AUC (AUC_p)² and partial AUC between two time-points (i.e., AUC_{t1-t2})³ to demonstrate the PK profile similarity between Qudexy XR™ QD and the reference drug Topamax ® BID during a 24-hour dosing interval at steady-state. Subsequently, upon the request by the OCP on November 13, 2013, the Sponsor submitted additional BE analysis results on November 20, 2013 for comparing the point-to-point topiramate plasma concentrations to further examine and assure the plasma profile similarity.

Results for *Pivotal Bioequivalence Study (study P09-003)*.

The table below (transcribed from Dr. Wu's review) presents values from routine bioequivalent analysis at steady state. This analysis also includes C_{min} . All values fulfill routine bioequivalent standards. I would also note the central analysis is close to 1.0 and the confidence intervals are relatively narrow for C_{max} and AUC; C_{min} value is only slightly divergent on this central analysis (C_{min} for IR, a little lower than XR).

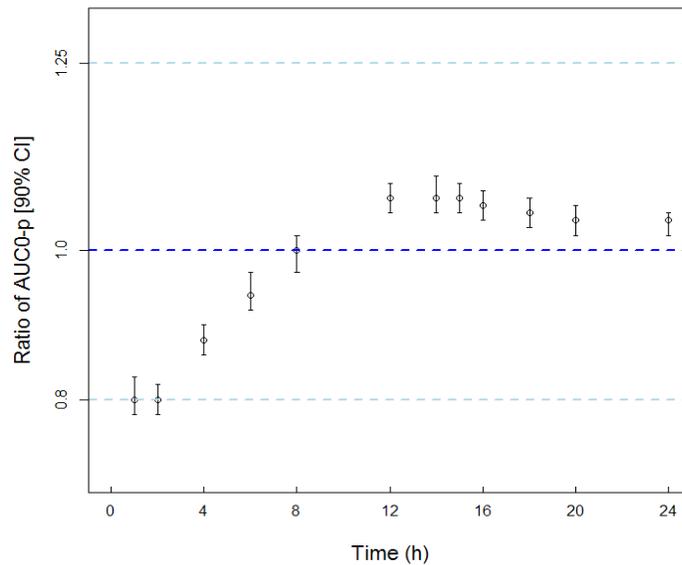
² Partial AUC (AUC_p) is the AUC from time point "0" to time point "p."

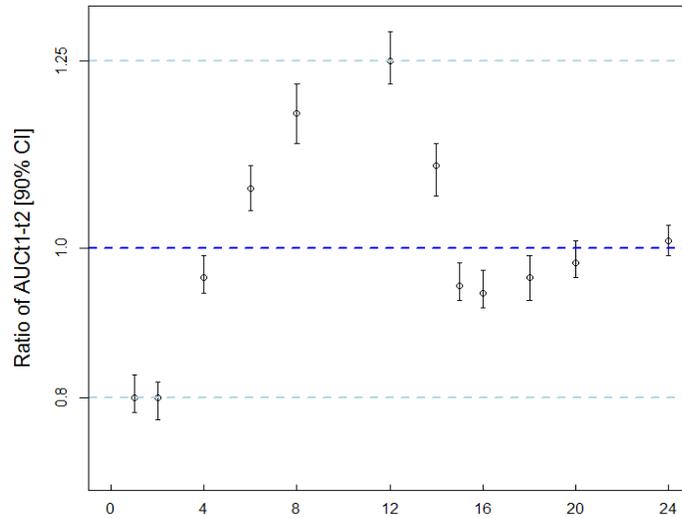
³ The partial AUC (AUC_{t1-t2}) is the AUC between two time points, "t1" and "t2."

Table. Statistical analysis for relative bioavailability of 200-mg dose of Brandname XR™ vs. Topamax® at steady-state

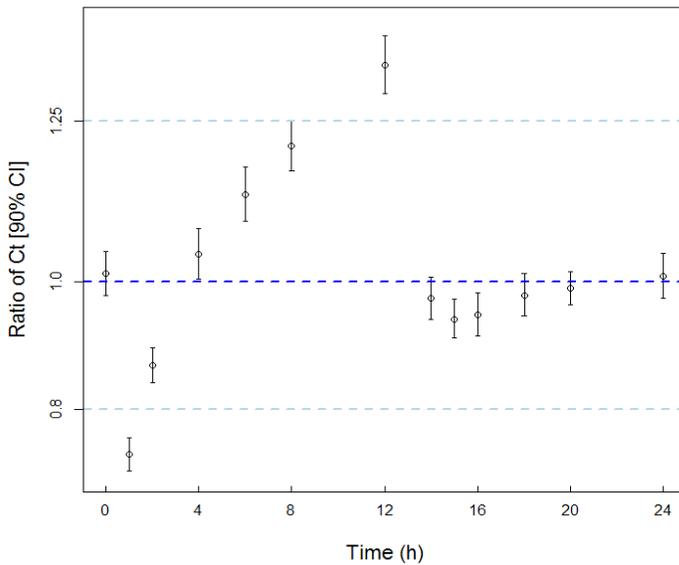
Parameter	N	USL255 (A) LS Mean	TOPAMAX® (B) LS Mean	Geometric Mean Ratio (A/B)	90% CI
AUC0-24h (µg·h/mL)	36	155	150	1.04	(1.02, 1.05)
Cmax,ss (µg/mL)	36	5.16	4.88	1.06	(1.03, 1.08)
Cmin,ss (µg/mL)	36	7.71	8.26	0.93	(0.90, 0.97)

The figures below (transcribed from Dr. Wu’s review) presents a comparison of mean partial AUC ratios (Qudexy XR/Topamax), and their 90% CI (indicated by bars). Horizontal lines represent the standard criteria for the ratio (0.8 to 1.25). Although not clear in his review, Dr. Wu clarified in discussions with me that this particular analysis was performed between the last dose of the first cross-over treatment (day14) and the last dose of the second cross-over treatment (day 28). It is apparent from these figures that bioequivalence ratio and confidence intervals in all but 2 to 3 cases lay within the standard bioequivalence requirements: i.e. 90% confidence intervals lie within the range of 0.80 to 1.25. Dr. Wu notes that “these deviations are not considered clinically significant.”





The figure below presents a point-to-point concentration comparison of bioequivalence. All but two points met bioequivalence standards. Dr. Wu’s interpretation of this was the same as above, i.e. no significant difference.



During the review, Dr. Wu expressed the opinion that because there were so many points in the analysis for the two types of partial AUCs, that the application could potentially be approved. However, sometimes after the approval of Trokendi,⁴ which included a label that described a point-to-point concentration analysis, the Division requested that the Sponsor provide such a point-to-point concentration evaluation (11/13/13) as an additional supportive analysis.

⁴ Trokendi was approved on 8/16/13.

Supportive Bioequivalent Study (P255-103)

The Sponsor performed a similar evaluation at a steady state concentration for the 200 mg dose in this study. Results were similar to that observed in the pivotal trial. Dr. Wu concludes that “given results of the relative BA comparison from this study.” Patients may be switched from immediate-release topiramate products to Qudexy XR™ at the same daily dose.

Conclusions

Drs. Wu and Men believe that these studies indicate the bioequivalence of the Sponsor’s product to the IR RLD. I agree. I would add this additionally supports the contention that the shape of the curves are equivalent, in that most points in the analyses fulfill the criteria of routine bioequivalent standards (confidence interval falls within the ratio 80-125%).

Other PK considerations

Dr. Wu found no other significant PK issues. He noted that the Sponsor’s product exhibits relatively linear absorption. No significant effect of a high fat meal was observed on absorption. Consumption of the contents of the capsules sprinkled on apple sauce demonstrated similar bioavailability to that of swallowing the capsule whole.

Of importance Dr. Wu discussed the issue raised by biopharmaceuticals, of the potential for a change in bioavailability, based upon dissolution studies at high alcohol concentrations. Dr. Wu does not believe that these data suggest a significant alcohol effect on bioavailability based upon under normal recreational use: 1) the dissolution differences is principally observed at high (40%) alcohol concentrations, 2) alcohol is rapidly absorbed and diluted in the GI tract, 3) topiramate is rapidly absorbed from the GI tract. I agree with his analysis. Nonetheless, pharmacodynamic interactions (risk of synergy of CNS depression) will be noted in the label, along with other CNS depressants.

Inspections

The site of the pivotal bioequivalence study (study P09-003) was inspected. As per Mr. Li’s, the OSI reviewer, the inspection/audit indicated the site and data generated were “acceptable.”

6. Clinical Microbiology

Does not apply.

7. Clinical/Statistical- Efficacy

Dr. Dinsmore performed the clinical review and Dr. Siddiqui performed the statistical review.

The principal decision of efficacy is founded on the PK analysis (see above). However, results from the controlled trial serve as supportive, but not essential, evidence of efficacy. The trial consisted of a single randomized, multicenter, double-blind, placebo-controlled, parallel-group phase 3 clinical trial that compares placebo to the lowest recommended daily dose (200 mg daily) in patients with “refractory⁵” partial-onset seizure with or without secondary generalization in adults (≥ 18 years of age). The study design was typical for such studies, except for having an interim blinded analysis for the determinations of the adequacy of sample size (see below). Patients entered a baseline/screening phase. Patients who met study requirements during this phase were then randomized and entered a 3 week Titration Phase. In this phase patients were started on 50 mg daily and titrated weekly by 50 mg/day per week until the final achievement of a dose of 200 mg daily, which took 3 weeks. This is similar to the labeled titration rate, except weekly rates can be 25 to 50 mg increments each week. Following the 3 week Titration Phase patients enter an 8 week Maintenance Phase.

The primary efficacy endpoint in the study was the percent reduction from Baseline in weekly (7-day) partial-onset seizure frequency during the Titration + Maintenance Phase. The intent-to-treat (ITT) population, was used as the primary analysis, and was defined as all subjects who were randomly assigned, received at least 1 dose of study drug, and had at least 1 post randomization seizure data point. The primary analysis used the Wilcoxon rank-sum test (WRST). Sensitivity analysis included a parametric ANCOVA analysis of logarithmically transformed change in seizure frequency data with the geographic region as a class variable, and baseline weekly partial-onset seizure frequency as a continuous covariate. This is a parametric alternative analysis that will generally correct data so that it is not normally distributed.

In total 124 and 125 patients were randomized to the drug and placebo groups, respectively with 17 % and 9% discontinuing before study completion in the drug and placebo groups , respectively. Approximately half of the patients who discontinued in the drug group did so for adverse events, whereas about 25 % of those discontinuing in the placebo group did so for adverse events.

The treatment groups were comparable with respect to demographics and baseline characteristics. Such characteristics included, sex, age, race, and baseline seizure frequency.

The results of the primary analysis are presented in the table below⁶.

	USL 255	Placebo	P value (WRST)
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⁵ In this study refractory was defined by the inclusion criteria of: 1) on a stable dosing regimen of 1 to 3 AEDs for at least 4-weeks prior to Visit (VNS or supplemental intermittent benzodiazepines was counted as a drug), 2) have a minimum of 8 partial-onset seizures and no more than 21 consecutive seizure free days, during the 8-week baseline.

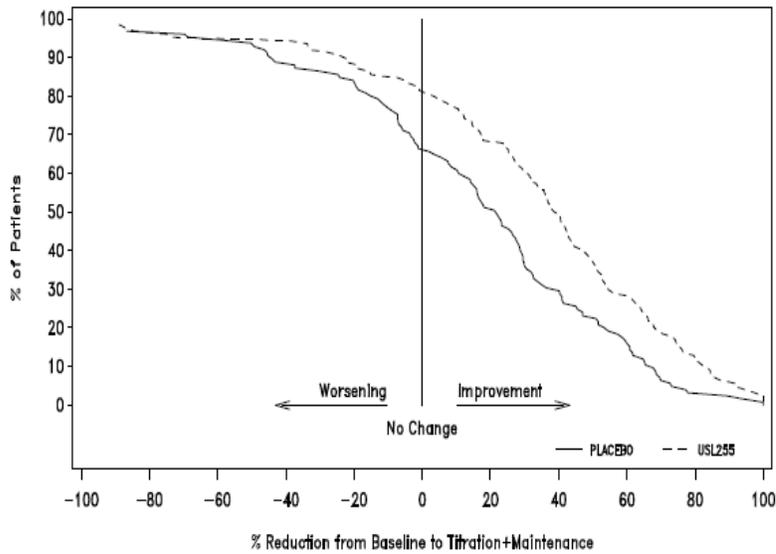
⁶ Although cross study comparisons are replete with caveats, it should be noted that the magnitude of effect observed with the present product is similar to that of the RLD at the same daily dose.

N	124	125	
Median: Percent Change from Baseline	39.50	21.65	<0.001

The ANCOVA Sensitivity analysis also revealed a significant difference between the experimental groups. No significant interaction was observed between geographic regions.

CDF analysis of percent reduction from baseline revealed an obvious separation between both groups (see below).

Partial-Onset Seizure Frequency Percent Reduction from Baseline to Titration Plus Maintenance by Patient Percentage, ITT Efficacy Population



A secondary endpoint, 50% responder rate, also revealed a statistically significant reduction associated with drug treatment.

To examine the impact of dropouts the Sponsor examined differences in seizure control the first and second 4 week epochs during maintenance. Little or no difference was appreciated. Moreover, this analysis suggests there is little tachyphylaxis of effect.

Dr. Siddiqui reanalyzed the Sponsor’s data and noted that he was able to reproduce results.

Dr. Siddiqui performed his own qualitative comparison of seizure reductions geographic, sex, age, and race subgroups, and demonstrated a trend toward therapeutic effect for in all groups.

Dr. Siddiqui concluded that the study provided “robust statistical and clinical evidence for the efficacy.” Dr. Dinsmore noted the statistically significant difference between both treatment arms.

I would add that, as noted above, the primary basis of efficacy for this NDA is the PK study (as described above), and the phase 3 study is considered to be supportive. The present conclusion is consistent with that analysis.

8. Safety

This application predominately depends upon safety data for the reference proprietary drug, Topamax, considering the determination of bioequivalence to that product. Additional safety, however, was submitted, and reviewed by the Medical Officer, Dr. Steven Dinsmore. The principal part of this data relied upon was from the randomized pivotal efficacy described above (p09-004) that compared 124 patients on Qudexy XR 200 mg/day to 125 to placebo. An additional long term extension phase to this study was also reviewed (study P09-005), which examined 210 patients (not unique to the latter study). Additional single dose and short term multiple dose PK studies in healthy volunteers were also included (n=352). In patient studies at least 133 patients received Qudexy XR for 6 months and 71 patients for one year.

Deaths

No deaths were reported in the Phase 1 studies. One death occurred as a result from an ischemic cerebral vascular event during the open label phase in a 54 year old male in the Phase 3 studies. This patient had risk factors and the event was not thought drug related by Dr. Dinsmore. I agree.

Serious Adverse Events (SAE)

Three subjects in the Phase 1 studies, all in single dose studies, experienced an SAE. This included one case of anemia, one of fractured arm and a spontaneous abortion. Considering what is known about the drug (Class D pregnancy risk) and the single exposure, Dr. Dinsmore notes that causality in the case of the spontaneous abortion is “uncertain.” Attribution for anemia, considering this is a single dose and single patient, is also uncertain, but I believe is unlikely related to the drug.

Two patients in each of the two experimental groups, placebo and drug, of the controlled Phase 3 study were reported to have SAEs. The SAEs for the topiramate group included physical assault and lobar pneumonia. These events, in my and Dr. Dinsmore’s view, were likely not related to drug treatment.

Fifteen SAEs were reported in the phase 3 open label extension study. Dr. Dinsmore examined these in detail. Thus, there were two reports of biliary ailments (one classified as cholelithiasis and the other as cholecystitis). Dr. Dinsmore notes that while the incidence is high in this study, the disorder is rather common in the population and a literature search did not reveal a signal. I would also note this is not a signal that has been identified in other studies. Other SAE, many of which were single isolated events, were identified including intervertebral disc protrusion, ischemic stroke (see above), diarrhea, pneumonia (2 events), fractures (2), headache, appendicitis, epilepsy related event (2) and acute psychosis. Dr. Dinsmore notes that some of these events are likely not attributed to the drug (disc protrusion,

appendicitis epilepsy related events). Others are already noted in the label, most in the section “Other Adverse Reactions Observed during Double-Blind Epilepsy Adjunctive Therapy Trials.” Of course, it is difficult to determine attribution in the reporting of one or two common isolated SAE in a small open label. These results study, in my and Dr. Dinsmore’s opinion, does not call for a change in the label.

Dropouts and Discontinuations

In Phase 1 studies, one patient discontinued because of a spontaneous abortion; this case is discussed above. An additional patient was discontinued because of a mild macular rash. Rashes are noted in the topiramate label.

Discontinuations because of AEs were more common in the drug treated, than the placebo treated group in the phase 3 controlled study, with 8.9% discontinuing with drug and 4.0% with placebo. Reasons for dropping out, not observed in the placebo group, in the drug group included disturbance in attention, somnolence, aphasia, depression suicidal, dizziness, drug intolerance, headache, irritability mental impairment, psychomotor retardation, rash, tension headache, and thinking abnormal. Most of these adverse events are already noted in the label. Many events occurred in only a single patient. This information does not indicate any change in labeling is required. Twelve percent of patients discontinued in the open label studies. Many of these events are known to be associated with topiramate and/or involved neurotoxicity (somnolence, dizziness, irritability mental impairment, fatigue, suicidal ideation). These events did not add any additional safety signal that is not already included in the label topiramate label.

In summary, Dr. Dinsmore concludes that none of these events “reveal a new safety signal,” and I agree with him.

Common Adverse Events

Thirty six to 47 percent of subjects reported adverse events in the phase 1 trials. The most commonly reported treatment emergent adverse events (TEAEs) that occurred in > 10.0% of subjects were paresthesia (24.8%), headache (18.1%), constipation (17.1%), somnolence (13.3%), diarrhea (12.4%), insomnia (12.4%), weight decreased (11.4%), and dry eye (10.5%).

In the phase 3 controlled trial study, the drug group exhibited a slightly greater rate of AEs than did the placebo group with 66.1% versus 52.8% of events reported in the former and latter groups, respectively. Common adverse reactions observed in the placebo controlled trial were similar to that observed for brand name immediate release formulation. Dr. Dinsmore notes that the most common adverse events, as calculated by treatment effect (drug-placebo) were somnolence, dizziness, paresthesia, weight decreased and fatigue. These events were qualitatively similar to the referenced labeled drug. A quantitative comparison to the referenced labeled drug is difficult because of the pitfalls of cross study comparison. Moreover, the only labeled data available for comparison to the reference drug combines a daily dose of 200 and 400 mg. The present study was performed at a daily dose of 200 mg.

Of interest there was one study in normal patients that utilized a crossover design and was designed to compare cognitive changes at steady state in patients treated with the reference label drug to Qudexy XR, but whose data were leveraged to examine bioequivalence (study P255-103). The Sponsor notes that cognitive analyses in this study were not available, but will be included in a follow-up report. Examination of adverse event reporting by preferred term, presented in Dr. Dinsmore's review, does not indicate a significant difference between both product.

Laboratory Findings

Bicarbonate

Based upon the phase 3 controlled trials, Qudexy XR produced a hyperchlorimic acidosis consistent with this drug's capacity to inhibit carbonic anhydrase and within the range experienced for the reference product, considering the low dose exposures. Thus, there was a reduction in bicarbonate of 3.5 mEq/L and mean increase in chloride of 3.7 mEq/L. The label describes similar bicarbonate reductions with 400 mg/exposures. Dr. Dinsmore notes these changes are not unexpected. Outlier analysis for bicarbonate also indicated some decrease. Dr. Dinsmore also notes a mild signal in the outlier data to reductions in serum potassium. He notes that such shifts are "minor." This observation is already described in the label of the referenced label drug. Dr. Dinsmore did not note any other serum chemistry signal.

Dr. Dinsmore examined the changes in indices for the complete blood count. In general, no obvious or consistent changes were observed in major indices. He, however, notes a minor increase Red Cell Distribution Width (RDW). He notes that the "RDW is based on an automated measurement of red blood cell size and is a quantitative indicator of anisocytosis." Dr. Dinsmore notes that "interpretation of the above observations (RDW) is uncertain." These were based on the absence of abnormalities in other indices, or other clinical evidence of a problem. I agree.

Vital Signs

Patients in the drug group of the controlled trial lost on average 2.0 kg, compared to 0 in the placebo group. This effect is well known and described in the label of the RLD. No appreciable signal was observed for changes in blood pressure or heart rate.

EKG

Because this drug was first approved 18 years ago, a formal QT study had never been performed. Because of the absence of such a study, the Sponsor petitioned the FDA to have such a study waived. The waiver included an AERS database review, literature, ECG assessment from the Sponsor's database, etc. From this information QT-IRT concluded that a formal QT study would not be required.

The Sponsor, however, presents EKG data from a study with sequential single dose escalations, with the final dose of 1600 mg. The study included 60 patients, was blinded and contained a placebo arm (1:4, placebo: drug). Twelve lead EKGs were obtained at baseline and 6 times throughout the first 30 hours following dosing, which included triplicate recordings. No QT prolongation was apparent. If anything, according to Dr. Dinsmore the data suggests a possible decrease in QTc intervals with increasing dose, a phenomenon observed with other anticonvulsant agents, particularly those with sodium channel blocking activity. Dr. Dinsmore thoroughly investigated the issue shortening and determined that the magnitude of the change observed in the present study is not of clinical significance. (b) (4)



9. Advisory Committee Meeting

Not requested.

10. Pediatrics

The following describes PREA requirements that were agreed upon with PeRC in a meeting held on 1/29/14:

- Initial Monotherapy in patients with partial onset or primary generalized tonic-clonic seizures:
 - Waived: birth to up to 2 years old because studies are impossible or highly impracticable (because of the small number of patients and the difficulty diagnosing such age groups):
 - Deferred: 2 years up to 10 years old because the product is ready for approval in adults and this indication is still protected through exclusivity
 - Appropriately labeled: 10 years to up to 17 years>
- Adjunctive therapy in patients with partial onset seizures:
 - Waived: Birth to up to 1 month for POS because studies are impossible or highly impracticable (because of the small number of patients and the difficulty diagnosing such age groups)
 - Deferred: 1 month up to 2 years because the product is ready for approval in adults (the Sponsor will have to develop an age appropriate formulation to perform such studies)
 - Appropriately labeled: 2 years to up to 17 years



- Adjunctive therapy in patients with primary generalized tonic-clonic seizures or seizures associated with Lennox-Gastaut syndrome (LGS)
 - Waived: Birth to up to 2 years because studies are impossible or highly impracticable (because of the small number of patients and the difficulty diagnosing such age groups)
 - Appropriately labeled: 2 years to less than 17 years

11. Other Relevant Regulatory Issues

Initial information on Financial Disclosure was incomplete, providing only a single name for each study site. Dr. Dinsmore requested additional information, which was received on 7/17/13. Dr. Dinsmore concludes that “financial disclosure requirements have been adequately completed.”

Because approval of this product will be determined through bioequivalence, an onsite inspection of the single controlled efficacy safety site was not requested.

The proposed proprietary name, Qudexy XR, was reviewed with regard to promotional and safety issues, and found acceptable.

12. Labeling

See label provided to the Sponsor.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Approval.
- Risk Benefit Assessment: This risk benefit is no different from the referenced label drug.
- Recommendation for Postmarketing Risk Management Activities: None.
- Recommendation for other Postmarketing Study Commitments: None
- Recommended Comments to Applicant: None.

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/s/

NORMAN HERSHKOWITZ
03/11/2014