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APPLICATION NUMBER:

205122Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Eric Bastings, MD.
Subject	(Deputy) Division Director Summary Review
NDA/BLA #	205122/000
Applicant Name	Upsher-Smith Laboratories (USL)
Date of Submission	02/11/2013
PDUFA Goal Date	03/11/2014
Proprietary Name / Established (USAN) Name	Qudexy XR / Topiramate extended-release capsules
Dosage Forms / Strength	Oral Capsules / 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg
Proposed Indication(s)	1. Partial Onset Seizures: • Adjunctive Therapy: 2 years to adults • Monotherapy: 10 years to adults 2. Primary Generalized Tonic-Clonic Seizures: • Adjunctive Therapy: 2 years to adults • Monotherapy: 10 years to adults 3. Adjunctive treatment for seizures associated with Lennox- Gastaut, 2 years to adults
Action	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
CDTL Review	Norman Hershkowitz, MD, PhD
Medical Officer Review	Steven Dinsmore, MD
Statistical Review	Ohidul Siddiqui, Ph.D.
CMC Review	Charles Jewell, Ph.D.
Biopharmaceutics Review	Sandra Suarez Sharp, Ph.D.
Clinical Pharmacology Review	Ta-Chen Wu, Ph.D.
OSI	Michael Skelly, Ph.D.
OSE/DMEPA	Jacqueline Sheppard, Pharm.D. and Sue (Liu) Liu, Pharm.D.
Patient labeling (DMPP and OGDP)	Twanda Scales, RN, BSN, MSN/Ed., and Aline Moukhtara, RN, MPH

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader
OSE=Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
DMPP=Division of Medical Policy Programs
OPDP=Office of Prescription Drug Promotion

1. Introduction

Upsher-Smith Laboratories (USL) submitted a 505(b)(2) NDA for an extended release (XR) formulation of topiramate. The proposed tradename for the new product is Qudexy XR. I will use that name to describe the product throughout this document. Topamax, the drug referenced for this application, is approved as an immediate-release (IR) formulation for the following indications:

- Initial monotherapy in patients ≥ 2 years of age with partial onset or primary generalized tonic-clonic seizures
- Adjunctive therapy for adults and pediatric patients (2 to 16 years of age) with partial onset seizures or primary generalized tonic-clonic seizures, and in patients ≥ 2 years of age with seizures associated with Lennox-Gastaut syndrome
- Prophylaxis of migraine headache in adults.

For Qudexy XR, the applicant is asking for the same epilepsy indications as Topamax, but with the monotherapy epilepsy indication limited to patients 10 years of age and older, as the indication in younger patients is still under exclusivity protection. The applicant is not seeking an indication for migraine.

2. Background

Dr. Hershkowitz describes the regulatory history of this application in his memorandum. Briefly, the division met on several occasions with the applicant during the development program, and discussed the importance of assessing the bioequivalence of Qudexy XR and Topamax, the referenced drug, not only by comparing the Cmax, Cmin and AUC of the products, but also the shape of drug plasma concentration over time. The division asked the applicant to present an argument that approval could be based on pharmacokinetic comparability alone. Absent a compelling argument, the division indicated that a clinical efficacy study may be needed.

The applicant elected to both assess the pharmacokinetic comparability of Qudexy XR and Topamax, and conduct a clinical efficacy study with Qudexy XR.

As discussed below, the pharmacokinetic data/analyses were found to be sufficient to support approval of Qudexy XR, and the clinical study was not required for approval. However, as the report of the clinical study was submitted to the NDA, it had to be reviewed by the Agency during this review cycle.

3. CMC/Device

I concur with the conclusions reached by the chemistry reviewer and by the biopharmaceutics reviewer that there are no issues that preclude approval in their respective disciplines.

Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical information was reviewed for this application.

5. Clinical Pharmacology/Biopharmaceutics

As described by Dr. Hershkowitz and Dr. Wu, the applicant compared (in Study P09-003) the bioavailability of a 200 mg dose of Qudexy XR administered once daily with that of a 100 mg dose of Topamax administered twice daily. Dr. Wu notes that routine bioequivalence standards (based on AUC, Cmax and Cmin) were met between Qudexy XR and Topamax. In addition, point-to-point analyses and partial AUC analyses between multiple timepoints also support the bioequivalence of Qudexy XR and Topamax. Therefore, Study P09-003 provides the evidence necessary to bridge the safety and efficacy of Topamax to that of Qudexy XR, and constitutes the primary basis for approval of Qudexy XR.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

As discussed above, pharmacokinetic study P09-003 is the primary basis for approval of this application, as it allows a bridging of the safety and efficacy of Topamax to that of Qudexy XR.

The applicant also conducted Study P09-004, which examined the safety and efficacy of Qudexy XR in patients with refractory partial-onset seizure with or without secondary generalization in adults. In that study, patients treated with Qudexy XR had a significantly lower frequency of seizures than patients treated with placebo (median of 22 vs. 40 seizures per week, $p<0.001$).

8. Safety

As discussed above, the safety of Qudexy XR is supported by pharmacokinetic bridging with the immediate-release formulation of topiramate, and no new safety information was required to support approval. As the applicant conducted a safety and efficacy study in patients with "refractory" partial-onset seizure with or without secondary generalization, the Medical Officer reviewed the safety results of that study. No new safety signal was identified. Importantly, the study was not designed to compared the safety of Qudexy XR to that of other formulations of topiramate, and cross-study comparisons, with all of their usual pitfalls, are further limited by differences between the doses tested for Qudexy XR, and those described in labeling of other formulations of topiramate.

9. Advisory Committee Meeting

No advisory meeting was necessary for this 505(b)(2) application.

10. Pediatrics

PREA was triggered by this new formulation. In consultation with PeRC, the following decisions were made regarding pediatric studies for Qudexy XR:

1. 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
- 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

2. Adjunctive therapy in patients with partial onset seizures:
- Waived: birth to up to 1 month for POS because studies are impossible or highly impracticable
- Deferred: 1 month up to 2 years because the product is ready for approval in adults
- Appropriately labeled: 2 years to up to 17 years

3. Adjunctive therapy in patients with primary generalized tonic-clonic seizures or seizures associated with Lennox-Gastaut syndrome: this indication is orphan and exempt from PREA requirements.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

Study P09-003 was audited by the Office of Scientific Investigations. Data were found to be acceptable.

12. Labeling

The proposed proprietary name, Qudexy XR, was found acceptable. There are no unresolved labeling issues.

13. Decision/Action/Risk Benefit Assessment

As bioequivalence was established between the referenced drug and Qudexy XR, I will issue an approval letter, with the following post-marketing requirements:

2137-1 Develop an age appropriate formulation of Qudexy XR (topiramate) extended-release capsules that can be used in children ages 1 month to less than 2 years old.

2137-2 A study to evaluate the pharmacokinetics and tolerability of the age-appropriate formulation of Qudexy XR (topiramate) extended-release capsules, developed in PMR 2137-1, as adjunctive therapy in children ages 1 month to less than 2 years with partial onset seizures (POS).

2137-3 An adequately controlled study to assess the efficacy and safety of the age-appropriate formulation of Qudexy XR (topiramate) extended-release capsules, developed in PMR 2137-1, as adjunctive therapy in children ages 1 month to less than 2 years with POS.

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/s/

ERIC P BASTINGS
03/11/2014