

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205122Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

PATENT AND EXCLUSIVITY CERTIFICATIONS

Pursuant to the provisions of 21 U.S.C. 355(b)(2)(B) and 21 CFR 314.54(a)(1)(vi), Upsher-Smith Laboratories, Inc. (USL) makes the following statements with respect to patents listed in the FDA Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) for the reference listed drug, Topamax® (topiramate) Tablets, NDA 020505. The statements are provided in accordance with 21 CFR 314.50(i)(1)(iii)(A):

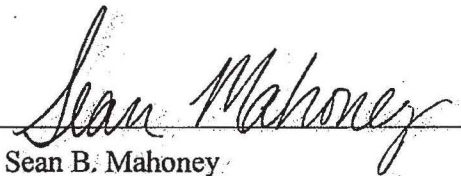
Statements Regarding Method of Use Patents

U.S. Patent 5,998,380 is a method of use patent listed in the Orange Book for Topamax® Tablets, NDA 020505, with **Patent Use Code U-598 Prophylactic Treatment of Migraine**. This method of use patent does not claim any of the proposed indications for Topiramate Extended-Release Capsules, for which this application is being submitted.

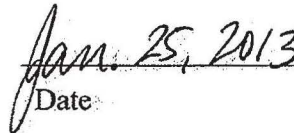
U.S. Patent 6,503,884 is a method of use patent listed in the Orange Book for Topamax® Tablets, NDA 020505, with **Patent Use Code U-598 Prophylactic Treatment of Migraine**. This method of use patent does not claim any of the proposed indications for Topiramate Extended-Release Capsules, for which this application is being submitted.

U.S. Patent 7,018,983 is a method of use patent listed in the Orange Book for Topamax® Tablets, NDA 020505, with **Patent Use Code U-723 Prophylactic Treatment of Migraine**. This method of use patent does not claim any of the proposed indications for Topiramate Extended-Release Capsules, for which this application is being submitted.

U.S. Patent 7,498,311 is a method of use patent listed in the Orange Book for Topamax® Tablets, NDA 020505, with **Patent Use Code U-955 Prophylactic Treatment of Migraine**. This method of use patent does not claim any of the proposed indications for Topiramate Extended-Release Capsules, for which this application is being submitted.



Sean B. Mahoney
Associate General Counsel, Intellectual Property


Date

PATENT AND EXCLUSIVITY CERTIFICATIONS

Exclusivity Statements

According to the information published in the FDA Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, as of January 25, 2012, the following unexpired Exclusivity Data pertaining to the reference listed drug product, Topamax® (topiramate) Tablets, NDA 020505, are listed:

- Exclusivity expires on **June 22, 2013**:

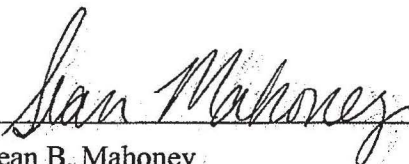
Exclusivity Code: PED (Pediatric Exclusivity)

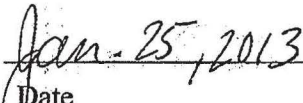
Indications for the corresponding pediatric population are not being pursued for the proposed USL255 Topiramate ER Capsules product; however, USL incorporated relevant safety information in its proposed labeling and USL understands that, unless a right of reference is provided, USL will not be able to obtain approval of its NDA prior to exclusivity expiration.

- Exclusivity expires on **July 15, 2014**:

Exclusivity Code: NPP (New Patient Population)

Indications for the corresponding patient population are not being pursued for the proposed USL255 Topiramate ER Capsules product; all corresponding labeling relevant to this patient population has been omitted from the proposed labeling.


Sean B. Mahoney
Associate General Counsel, Intellectual Property


Date

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 10/31/2016 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		NDA NUMBER 205122 NAME OF APPLICANT/NDA HOLDER Upsher-Smith Laboratories, Inc.	
The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.			
TRADE NAME (OR PROPOSED TRADE NAME) Qudexy XR			
ACTIVE INGREDIENT(S) Topiramate		STRENGTH(S) 25mg, 50mg, 100mg, 150mg, 200mg	
DOSAGE FORM Capsules			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number 8,652,527		b. Issue Date of Patent 02/18/2014	
		c. Expiration Date of Patent 3/19/2033	
d. Name of Patent Owner Upsher-Smith Laboratories, Inc.		Address (of Patent Owner) 6701 Evenstad Drive	
		City/State Maple Grove, MN	
		ZIP Code 55369	FAX Number (if available)
		Telephone Number 763-315-2000	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1.e.)	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No 			
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No 			

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). ☐ Yes ☐ No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) ☐ Yes ☒ No

2.6 Does the patent claim only an intermediate? ☐ Yes ☒ No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☒ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? ☒ Yes ☐ No

3.2 Does the patent claim only an intermediate? ☐ Yes ☒ No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

4.2 Patent Claim Number(s) (as listed in the patent): ☐ Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product: Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product: ☐ Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Sean Mahoney

Date Signed

02/19/2014

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder

☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

☒ Patent Owner

☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Sean B. Mahoney -- Associate General Counsel, Intellectual Property

Address

6701 Evenstad Drive

City/State

Maple Grove, MN

ZIP Code

55369

Telephone Number

763-315-2245

FAX Number (if available)

E-Mail Address (if available)

sean.mahoney@upsher-smith.com

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 20 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

EXCLUSIVITY SUMMARY

NDA # 205122

SUPPL #

HFD #

Trade Name Qudexy XR

Generic Name topiramate extended-release capsules

Applicant Name Upsher-Smith Laboratories, Inc.

Approval Date, If Known March 11, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The study conducted was a bioavailability study. For formulation bridging, studies P09-003 and 255-103 were conducted, both including steady-state pharmacokinetic studies and BA/BE comparing the proposed drug products with the reference listed drug Topamax immediate-release tablets.

The studies conducted (steady-state PK, bioavailability and bioequivalence) were sufficient for approval. The clinical studies conducted were not necessary to support approval of the application.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

n/a

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

(b) (4)

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☒ NO ☐

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No. The reference listed drug, Topamax[®] (20505) was granted pediatric exclusivity, which expired on June 22, 2013. Topamax[®] also received new patient population exclusivity, which expires on September 1, 2019.

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than

deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20844 Topamax[®] (topiramate) Sprinkle Capsules

NDA# 20505 Topamax[®] (topiramate) Tablets

NDA# 201635 Trokendi[®] XR extended-release capsules

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the

effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
IND # YES ☐ ! NO ☐
! Explain:

Investigation #1 !
 YES ☐ ! NO ☐
 Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

If yes, explain:

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

TAURA N HOLMES
03/03/2015

WILLIAM H Dunn
03/03/2015

Upsher-Smith Laboratories, Inc.
Original New Drug Application/NDA 205122
Topiramate Extended Release Capsules

DEBARMENT CERTIFICATION

Upsher-Smith Laboratories, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



Nancy VanGieson, MBA
ASQ CQA, CQE, CMoQ/OE, CSQE, CBA
Vice President, Quality and Corporate
Compliance/Chief Compliance Officer

1/21/13

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 205122 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Qudexy XR Established/Proper Name: topiramate Dosage Form: extended-release capsules		Applicant: Upsher-Smith Agent for Applicant (if applicable): Cynthia G. Farner
RPM: Taura Holmes, PharmD		Division: Division of Neurology Products
<u>NDA and NDA Efficacy Supplements:</u> NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.) <u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)): NDA 20844: Topamax® Sprinkle Capsules NDA 20505: Topamax® Tablets NDA 201635: Trokendi XR® extended-release Capsules Provide a brief explanation of how this product is different from the listed drug. This application provides for a new extended-release dosage form. The RLDs are immediate-release products. ☐ This application does not rely upon a listed drug. ☐ This application relies on literature. ☐ This application relies on a final OTC monograph. ☒ This application relies on (explain) an already approved IR product <u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u> <u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u> ☐ No changes ☐ Updated Date of check: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.		
❖ Actions		
- Proposed action - User Fee Goal Date is 03/11/14		☒ AP ☐ TA ☐ CR

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

Previous actions (<i>specify type and date for each action taken</i>)	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics³	
Review priority: ☒ Standard ☐ Priority Chemical classification (new NDAs only): ☐ Fast Track ☐ Rolling Review ☐ Orphan drug designation ☐ Rx-to-OTC full switch ☐ Rx-to-OTC partial switch ☐ Direct-to-OTC NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC ☐ Submitted in response to a Pediatric Written Request REMS: ☐ MedGuide ☐ Communication Plan ☐ ETASU ☐ MedGuide w/o REMS ☐ REMS not required Comments:	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	☐ Yes ☐ No
❖ Public communications (<i>approvals only</i>)	
Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☐ No
Press Office notified of action (by OEP)	☐ Yes ☐ No
Indicate what types (if any) of information dissemination are anticipated	☐ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i>	☒ No ☐ Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ No ☐ Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(i)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☒ (iii)
[505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☒ No paragraph III certification Date patent will expire not applicable, method of use patent
[505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i>	☒ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

☐ Yes ☐ No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

☐ Yes ☐ No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

☐ Yes ☐ No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). <i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i> <i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i>	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist⁴	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) 03/11/14 – Approval
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	03/06/14
• Original applicant-proposed labeling	02/11/13; 12/17/13
• Example of class labeling, if applicable	

⁴ Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	03/06/14
Original applicant-proposed labeling	02/11/13; 12/17/13
Example of class labeling, if applicable	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
Most-recent draft labeling	
❖ Proprietary Name - Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) - Review(s) (<i>indicate date(s)</i>) - Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.	Granted: 02/21/14 Review: 02/18/14
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	☐ RPM ☒ DMEPA 10/23/13; ☒ DMPP/PLT (DRISK) 01/30/14 ☒ OPDP (DDMAC) 02/10/14 ☐ SEALD ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	RPM Filing: 02/28/14
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	505(b)(2): 02/23/14 (Approval)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 01/11/14	☐ Not a (b)(2) ☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
Applicant is on the AIP	☐ Yes ☒ No
- This application is on the AIP - If yes, Center Director's Exception for Review memo (<i>indicate date</i>) - If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) - Date reviewed by PeRC 01/29/14 If PeRC review not necessary, explain: _____ - Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)	☐ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	☒ Verified, statement is acceptable

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	Information Requests: 2/21/14; 2/18/14; 1/16/14; 12/9/13; 12/4/13;
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	☐ No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☐ N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	☐ No mtg
• EOP2 meeting (<i>indicate date of mtg</i>)	☐ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☐ None
Division Director Summary Review (<i>indicate date for each review</i>)	☐ None
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☐ None
PMR/PMC Development Templates (<i>indicate total number</i>) : 3	☐ None
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	
• Clinical review(s) (<i>indicate date for each review</i>)	03/06/14
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See Clinical Review 03/06/14
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	☒ None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	☐ None requested 11/6/13

⁶ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	☐ None
Clinical Microbiology Review(s) (indicate date for each review)	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) (indicate date for each review)	☒ None
Statistical Team Leader Review(s) (indicate date for each review)	☒ None
Statistical Review(s) (indicate date for each review)	☐ None 01/24/2014
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	☐ None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	☒ None
Clinical Pharmacology review(s) (indicate date for each review)	☐ None 02/07/2014 05/03/2013
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	☐ None
Nonclinical ☒ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	☐ None
• Supervisory Review(s) (indicate date for each review)	☐ None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	☐ None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	☐ None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	☐ No carc
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	☐ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	☐ None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	☐ None Filing Review: 05/24/13
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	☐ None ONDQA: 04/22/13; 01/07/14; 01/16/14 Biopharm: 01/14/13
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review) ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (indicate date of each review)	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	☒ None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	
☐ Review & FONSI (<i>indicate date of review</i>)	
☐ Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷</i>)	Date completed: inspection (clinical: 7/16-7/19/13; bioanalytical: (b) (4)); in DARRTS 11/6/13 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication **AND** a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/

TAURA N HOLMES
03/03/2015



NDA 205122

GENERAL ADVICE

Upsher-Smith Laboratories, Inc.
Attention: Mark A. Cierpial, PhD, RAC
Qudexy XR Regulatory Lead
6701 Evenstad Drive
Maple Grove, MN 55369

Dear Dr. Cierpial:

Please refer to your New Drug Application (NDA) dated February 11, 2013, received February 11, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Qudexy XR (topiramate) extended-release capsules 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg.

[REDACTED] (b) (4)

We have reviewed the referenced material and conclude that the six studies listed in the Upsher-Smith Laboratories, Inc., (USL) original exclusivity request are bioavailability studies or pharmacokinetic studies that are supportive of the pivotal bioavailability study, P09-003. The FD&C Act (sections 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the FD&C Act) and FDA's regulations (21 CFR 314.108) expressly exclude bioavailability studies from studies that would support eligibility for [REDACTED] (b) (4) exclusivity. Consequently, the six studies listed in USL's original exclusivity request would not support your request for [REDACTED] (b) (4) exclusivity for Qudexy XR.

Although studies P09-004 and P09-005 are not bioavailability studies, they were not essential to the approval of NDA 205122. During the NDA review, the Division concluded that the pivotal bioavailability study, which is the pharmacokinetic study described in Section 12.6 of Qudexy XR's labeling, was sufficient to support approval, demonstrating that the drug provided "similar steady-state topiramate concentrations to immediate-release topiramate taken every 12 hours." Therefore, Qudexy XR would be expected to have an equivalent safety and effectiveness profile to immediate-release topiramate, based on the results of the pivotal bioavailability study alone. Thus, the Division finds that Study P09-004, while supportive, was not essential to the approval of NDA 205122. Furthermore, Study P09-005, an open-label safety extension study of Study P09-004, was also supportive of, but not essential to, the safety conclusions of Qudexy XR.

The basis of approval for Qudexy XR included: (1) clinical studies using an immediate-release formulation of topiramate and (2) the demonstration of the pharmacokinetic equivalence of Qudexy XR to the immediate-release topiramate through the pivotal bioavailability study. The

approved labeling for Qudexy XR is clear that the basis of approval did not include studies P09-004 and P09-005.

Accordingly, USL has not sponsored or conducted a new clinical investigation other than a bioavailability study that was essential to approval of NDA 205122. (b) (4)

If you have any questions, contact Taura Holmes, PharmD, Regulatory Project Manager, via email or telephone at Taura.Holmes@fda.hhs.gov or (301) 796-1932.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Acting Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

WILLIAM H Dunn
07/16/2014

Holmes, Taura

From: Mark Cierpial <MCierpial@[REDACTED] (b) (4)>
Sent: Friday, February 21, 2014 4:31 PM
To: Holmes, Taura
Cc: Ware, Jacqueline H; Daugherty, Susan B (CSO)
Subject: RE: *NDA 205122* Information Request (Carton and Container)

Thanks Taura, we'll get this turned around early next week.
Have a nice weekend,
Mark

From: Holmes, Taura [<mailto:Taura.Holmes@fda.hhs.gov>]
Sent: Friday, February 21, 2014 3:02 PM
To: Mark Cierpial
Cc: Ware, Jacqueline H; Daugherty, Susan B (CSO)
Subject: *NDA 205122* Information Request (Carton and Container)

Dear Mark,

I am forwarding the following request from the Medication Error reviewer for NDA 205122.

Container Labels and Carton Labeling

1. Utilize a different font for the proprietary name. The "Q" in Qudexy can be mistaken for an "O" in the current style type.
2. Ensure that the entire established name "topiramate extended-release capsules" is presented in the same font size.
3. The color schemes for the 25 mg and 150 mg strengths are similar in hue, and the color schemes for the 150 mg and 200 mg strengths are similar in hue. We recommend choosing colors further apart on the color spectrum to help prevent wrong strength selection errors. In addition, choose colors that do not overlap with the colors used for the proprietary name [REDACTED] (b) (4)
4. Where applicable, minimize or reduce the swirl graphic near the proprietary name as it can be distracting.
5. Where applicable, relocate the Upsher-Smith logo from the principle display panel (PDP) to the side panel. This would help reduce clutter on the PDP and give more prominence to other important on the label.
6. For the carton labeling, once the company logo is relocated to the side panel per recommendation 5 above, move the quantity and Rx only further down on the PDP to reduce clutter.

Please submit your response to this request in paper/electronic archival format as an amendment to NDA 205122. We also request that you email your response to me in advance of a formal, archival submission no later than **COB February 28, 2014**. Please note that both communications (both email & archive) must contain identical information.

Please feel free to contact me if you should have any questions or concerns.

Kind regards,
Taura

Taura Holmes, PharmD
Regulatory Project Manager
Food and Drug Administration

Office of Drug Evaluation I
Division of Neurology Products

Office: 301-796-1932

Fax: 301-796-9842

Email: taura.holmes@fda.hhs.gov

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/s/

TAURA N HOLMES
02/27/2014

Holmes, Taura

From: Mark Cierpial <MCierpial@ [REDACTED] (b) (4)>
Sent: Monday, February 10, 2014 5:02 PM
To: Holmes, Taura
Subject: RE: *NDA 205122* Information Request
Attachments: signed-form-0015.pdf; cover-0015-financial-disclosure-statement.pdf

Hello Taura –

Here is the requested submission. We will be sending this in formally through the gateway.

Thanks,
Mark

From: Holmes, Taura [<mailto:Taura.Holmes@fda.hhs.gov>]
Sent: Monday, February 10, 2014 12:55 PM
To: Mark Cierpial
Subject: *NDA 205122* Information Request

Dear Mark,

I am forwarding the following request from the Medical Officer:

We are in receipt of your updated form 3454. We acknowledge that this form indicates that no investigator is identified to have a financial conflict of interest. However, due to the close proximity of your NDA submission to the issuance of the recent guidance, "*Guidance for Clinical Investigators, Industry, and FDA Staff, Financial Disclosure by Clinical Investigators*," published in February 2013, we request a confirmatory statement that no clinical investigators were full or part time employees of Upsher-Smith Laboratories, Inc. For reference, a link to the guidance is below:

<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM341008.pdf>

Please submit your response to this request in paper/electronic archival format as an amendment to the above NDA (205122). It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

We ask that you please respond to this request by February 18, 2014.

If you have any questions, please let me know.

Kind regards,
Taura

Taura Holmes, PharmD
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I
Division of Neurology Products

Office: 301-796-1932
Fax: 301-796-9842

Email: taura.holmes@fda.hhs.gov

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/s/

TAURA N HOLMES
02/27/2014

Holmes, Taura

From: Mark Cierpial <MCierpial@ [REDACTED] (b) (4)>
Sent: Friday, January 17, 2014 3:13 PM
To: Holmes, Taura
Cc: Daugherty, Susan B (CSO); Ware, Jacqueline H
Subject: RE: *NDA 205122* Information Request (Carton and Container)
Attachments: Carton & Bottle Label Artwork 17Jan14.zip.html

Follow Up Flag: Follow up
Due By: Thursday, January 23, 2014 11:00 AM
Flag Status: Completed

Hi again Taura –

I'm not sure if you need these or not, but thought I'd send them just in case. These are the same files that we submitted to the application in Sequence 0014, they just open differently (clean rather than with mark-up that can be toggled on and off). Since this content is already in the application, I wasn't intending to submit formally as a new Sequence. Can you confirm that this is okay?

Have a nice weekend!
Mark

From: Mark Cierpial
Sent: Thursday, January 16, 2014 2:31 PM
To: 'Holmes, Taura'
Cc: Daugherty, Susan B (CSO); Ware, Jacqueline H
Subject: RE: *NDA 205122* Information Request (Carton and Container)

Hi Taura –

The pdfs are dynamic in that the reviewer can view as much or as little of the information content as desired. Each pdf will open with all content showing, but the view can be modified by deselecting whatever information layers you don't want to see (see example attached).

Let me know if you need any further assistance with this.

Kind regards,
Mark

From: Holmes, Taura [<mailto:Taura.Holmes@fda.hhs.gov>]
Sent: Thursday, January 16, 2014 12:06 PM
To: Mark Cierpial
Cc: Daugherty, Susan B (CSO); Ware, Jacqueline H
Subject: *NDA 205122* Information Request (Carton and Container)

Dear Mark,

I am forwarding the following request from the Medication Error reviewer for NDA 205122.

Please submit a "clean" copy of the proposed container and carton labels for USL255 by COB January 21, 2014.

Please submit your response to this request in paper/electronic archival format as an amendment to NDA 205122. We also request that you email your response to me in advance of a formal, archival submission. Please note that both communications (both email & archive) must contain identical information.

Please feel free to contact me if you should have any questions or concerns.

Kind regards,
Taura

Taura Holmes, PharmD
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I
Division of Neurology Products

Office: 301-796-1932
Fax: 301-796-9842
Email: taura.holmes@fda.hhs.gov

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/s/

TAURA N HOLMES
02/27/2014

Holmes, Taura

From: Mark Cierpial <MCierpial@[REDACTED]> (b) (4)
Sent: Friday, January 10, 2014 2:02 PM
To: Holmes, Taura
Cc: Daugherty, Susan B (CSO); Ware, Jacqueline H
Subject: RE: *NDA 205122* Information Request (Container label and Carton labeling)

Thanks Taura – have a nice weekend.

From: Holmes, Taura [mailto:Taura.Holmes@fda.hhs.gov]
Sent: Friday, January 10, 2014 1:59 PM
To: Mark Cierpial
Cc: Daugherty, Susan B (CSO); Ware, Jacqueline H
Subject: RE: *NDA 205122* Information Request (Container label and Carton labeling)

Dear Mark,

All changes should be incorporated in the new submission. January 15, 2014, is the requested date for the emailed response. We ask that you submit your formal, archival submission no later than the close of business January 21, 2014.

Please note that both communications (both email & archive) must contain identical information.

Kind regards,
Taura

From: Mark Cierpial [mailto:MCierpial@[REDACTED]] (b) (4)
Sent: Thursday, January 09, 2014 4:12 PM
To: Holmes, Taura
Cc: Daugherty, Susan B (CSO); Ware, Jacqueline H
Subject: RE: *NDA 205122* Information Request (Container label and Carton labeling)

Hello Taura –

Thank you for this, we'll get right on it.

Would it be acceptable to update and submit one representative set of labels and labeling by the 15th, to be followed up by the rest of the components (ie, dosage strengths), or does the Agency need to see all the components revised by the 15th?

We're not sure how far along DMEPA is with the review of new proposed trade name (Qudexy XR), but we plan to update the labels and labeling to reflect this new name.

Finally, I'm assuming the January 15th requested date is for the emailed response, correct?

Kind regards,
Mark

Mark A. Cierpial, PhD, RAC
USL255 Regulatory Lead
919.899.9269

From: Holmes, Taura [<mailto:Taura.Holmes@fda.hhs.gov>]
Sent: Thursday, January 09, 2014 2:09 PM
To: Mark Cierpial
Cc: Daugherty, Susan B (CSO); Ware, Jacqueline H
Subject: *NDA 205122* Information Request (Container label and Carton labeling)

Dear Mark,

I am forwarding the following recommendations from the Medication Error reviewer for NDA 205122. Please update container labels and carton labeling in accordance with these recommendations.

A. All Container Labels and Carton Labeling (all strengths and net quantities)

1. Revise the presentation of the proprietary name from all capitals to title case in order to improve the readability of the name.
2. We recommend choosing a more prominent color for the 'XR' in the proprietary name or consider switching the use of color in the proprietary name (b) (4)
3. Ensure that the established name has a prominence commensurate with the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
4. Revise the statement (b) (4) to read similar to "Administer dose once daily. See package insert for full prescribing information."
5. As currently presented, there is inadequate strength differentiation within the product line. (b) (4)

(b) (4) We recommend you choose colors for the labels and labeling that are completely different from the capsule colors and adequately different from each other.

B. Container Labels (all strengths and net quantities)

1. Increase the size and prominence of the statement "Once-Daily Dosing" by increasing the font size and moving it above the proprietary name to accommodate this revision.
2. Decrease the font size of the "Rx only" statement and debold the statement.
3. If space permits, relocate the "Dispense the accompanying Medication Guide to each patient" statement to beneath the strength, similar to the container labels for the 100 mg strength.

C. Carton Labeling (all strengths and net quantities)

(b) (4)

Please submit your response to this request in paper/electronic archival format as an amendment to NDA 205122. We also request that you email your response to me in advance of a formal, archival submission. Please note that both communications (both email & archive) must contain identical information.

We ask that you respond no later than the close of business January 15, 2014.

Please feel free to contact me if you should have any questions or concerns.

Kind regards,
Taura

Taura Holmes, PharmD

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I
Division of Neurology Products

Office: 301-796-1932

Fax: 301-796-9842

Email: taura.holmes@fda.hhs.gov

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/s/

TAURA N HOLMES
02/27/2014

Holmes, Taura

From: Mark Cierpial <MCierpial@ [REDACTED] (b) (4)>
Sent: Thursday, December 19, 2013 11:08 AM
To: Holmes, Taura
Subject: RE: *NDA 205122* Information Request

Thanks Taura,
Besides myself, we had Sandra Croak-Brossman, Senior Director, Regulatory Affairs and Jennifer McGoogan, Regulatory Affairs Manager – Labeling
All the best,
Mark

From: Holmes, Taura [mailto:Taura.Holmes@fda.hhs.gov]
Sent: Thursday, December 19, 2013 11:04 AM
To: Mark Cierpial
Cc: Daugherty, Susan B (CSO)
Subject: RE: *NDA 205122* Information Request

Dear Mark,

The following individuals were in attendance at the December 11, 2013, teleconference:

Susan Daugherty, RN, BSN, Senior Regulatory Project Manager
Heather Bullock, RN, BSN, Regulatory Project Manager
Taura Holmes, PharmD, Regulatory Project Manager

Could you please send me the names of the individuals from Upsher Smith Laboratories who were on the December 11, 2013, teleconference as well?

Have a nice holiday as well!

Kind regards,
Taura

From: Mark Cierpial [mailto:MCierpial@ [REDACTED] (b) (4)>
Sent: Thursday, December 19, 2013 10:39 AM
To: Holmes, Taura
Subject: RE: *NDA 205122* Information Request

Thanks Taura. Could you send me the names of the individuals who were on the 11 Dec 2013 teleconference with us.
Have a nice holiday!
Mark

From: Holmes, Taura [mailto:Taura.Holmes@fda.hhs.gov]
Sent: Tuesday, December 17, 2013 3:23 PM
To: Mark Cierpial
Cc: Be.Stangler@upsher-smith.com; Daugherty, Susan B (CSO)
Subject: RE: *NDA 205122* Information Request

Dear Mark,

I confirm receipt of your submission dated December 16, 2013.

Kind regards,
Taura

From: Mark Cierpial [<mailto:MCierpial@> (b) (4)]
Sent: Monday, December 16, 2013 4:18 PM
To: Holmes, Taura
Cc: Be.Stangler@upsher-smith.com
Subject: *NDA 205122* Information Request

Good afternoon Taura –

We've completed the label revision requested during our teleconference last week. I've attached the document along with the submission cover letter. As always, we will submit this formally to the NDA via the gateway.

Kind regards,
Mark

From: Holmes, Taura
Sent: Monday, December 09, 2013 2:44 PM
To: 'Mark Cierpial'
Subject: RE: *NDA 205122* Information Request

Dear Mark,

I confirm receipt of your email dated December 8, 2013.

A representative from the Division's review team would like to briefly speak with you regarding your December 8, 2013, submission. Are you available December 10, 2013, during either of the following times?

1. 1:00-1:30 PM EST
2. 1:30-2:00 PM EST

Kind regards,
Taura

Taura Holmes, PharmD
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I
Division of Neurology Products

Office: 301-796-1932
Fax: 301-796-9842
Email: taura.holmes@fda.hhs.gov

From: Mark Cierpial [<mailto:MCierpial@> (b) (4)]
Sent: Sunday, December 08, 2013 4:51 PM
To: Holmes, Taura

Cc: Daugherty, Susan B (CSO); Ware, Jacqueline H
Subject: RE: *NDA 205122* Information Request

Good afternoon Taura –

We went through the draft USL255 label again this weekend to confirm that all appropriate Section numbers matched with what is in the Trokendi XR label. We did find one error, which I believe you also mentioned on the phone; that is, our current Section 12.4 should be numbered 12.6, as Sections 12.4 and 12.5 are reserved for “Microbiology” and “Pharmacogenomics,” respectively. We propose making this correction in the next round of revisions.

I’ve also attached a document that might be of assistance to you. It is a three-way comparison of our proposed labeling, the Trokendi XR label, and the Topamax label. All of the content matches up across rows so you can easily see where changes, additions and/or deletions have been made. For example, in this document it is easy to see that we have deleted the Trokendi XR Section 5.4 Warning regarding “Interactions with Alcohol,” and that, although our Section 5.4 is now “Suicidal Ideation and Behavior” (like the Topamax label), the content is the same (unless indicated in the redline version you requested previously). Note that we did not skip Section number 5.4, as the Warnings and Precautions section of the label does not have reserved numbers, per our reading of the guidance.

Hopefully this document will be a helpful tool for you. If you would like us to submit it formally to the NDA, please let me know.

Kind regards,
Mark

From: Holmes, Taura [<mailto:Taura.Holmes@fda.hhs.gov>]
Sent: Friday, December 06, 2013 2:17 PM
To: Mark Cierpial
Cc: Daugherty, Susan B (CSO); Be.Stangler@upsher-smith.com; Ware, Jacqueline H
Subject: RE: *NDA 205122* Information Request
Importance: High

Good afternoon Mark,

I confirm receipt of your December 6, 2013, submission in response to the Agency’s December 4, 2013, information request. Please note that the approved Trokendi XR labeling represents the Agency’s current thinking. In order to facilitate further review of your application, we request that you resubmit your labeling in accordance with the Agency’s December 4, 2013, information request. Your labeling should mimic the approved Trokendi XR labeling to include all sections as well as the organizational format in the approved Trokendi XR labeling.

We request that you send updated labeling via email by the close of business today as our labeling discussions begin Monday, December 9, 2013.

Kind regards,
Taura

Taura Holmes, PharmD
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I
Division of Neurology Products

Office: 301-796-1932
Fax: 301-796-9842
Email: taura.holmes@fda.hhs.gov

From: Mark Cierpial [<mailto:MCierpial@> (b) (4)]
Sent: Friday, December 06, 2013 11:00 AM
To: Holmes, Taura
Cc: Daugherty, Susan B (CSO); Be.Stangler@upsher-smith.com
Subject: RE: *NDA 205122* Information Request

Good morning Taura –

Please find attached our responses to your requests of 04 Dec 2013. We will submit these documents formally as NDA Sequence 0012 early next week.

Kind regards,
Mark

From: Holmes, Taura [<mailto:Taura.Holmes@fda.hhs.gov>]
Sent: Wednesday, December 04, 2013 4:42 PM
To: Mark Cierpial
Cc: Daugherty, Susan B (CSO)
Subject: *NDA 205122* Information Request
Importance: High

Dear Mark,

Below are requests from the review team related to their ongoing review of NDA 205122.

1. We note that the organization of the subsections within your December 2, 2013, label is not consistent with the subsection organization within the approved Trokendi XR label. Using the approved Trokendi XR label as a guide, please provide updated draft labeling which follows the same section and subsection format as the Trokendi XR label. For example, subsection 2.1 of the Trokendi XR label is Monotherapy Use; however, this subsection is located in subsection 1.1 of your label. We request that you relocate subsection 1.1 (Monotherapy) of your label to subsection 2.1 of your label. We also request that you relocate and/or reorganize the additional affected subsections.
2. Please ensure that each summarized statement or topic in the Highlights (HL) section references the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information.
3. Please format the Table of Contents (TOC) columns to read down then across even if the TOC is split across multiple pages. The following link should provide additional assistance:
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. In addition, please see Appendix A of the Selected Requirements of Prescribing Information (SRPI).

Please submit your response to this request in paper/electronic archival format as an amendment to NDA 205122. We also request that you email your response to me in advance of a formal, archival submission. Please note that both communications (email & archive) must contain identical information.

We ask that you please respond to this request no later than 12PM on December 6, 2013.

Please feel free to contact me if you should have any questions or concerns.

Kind regards,
Taura

Taura Holmes, PharmD
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I
Division of Neurology Products

Office: 301-796-1932

Fax: 301-796-9842

Email: taura.holmes@fda.hhs.gov

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/s/

TAURA N HOLMES
02/27/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 205122

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Upsher-Smith Laboratories, Inc.
6701 Evenstad Drive
Maple Grove, MN 55369

ATTENTION: Sandra J Croak-Brossman, PhD
Senior Director, Regulatory Affairs

Dear Dr. Croak-Brossman:

Please refer to your New Drug Application (NDA) dated and received February, 11, 2013, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Topiramate Extended-Release Capsules, 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg.

We also refer to your correspondence, dated and received December 4, 2013, requesting review of your proposed proprietary name, Qudexy XR. We have completed our review of the proposed proprietary name, Qudexy XR, and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your December 4, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Ermias Zerislassie, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0097. For any other information regarding this application, contact Taura Holmes, Regulatory Project Manager, in the Office of New Drugs at (301) 796-1932.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
02/21/2014

PeRC PREA Subcommittee Meeting Minutes
January 29, 2014

PeRC Members Attending:

Lynne Yao

Rosemary Addy

Hari Cheryl Sachs (Did not review (b) (4))

George Greeley

Robert “Skip” Nelson

Jane Inglese

Wiley Chambers (Did not review Topiramate, (b) (4))

Tom Smith

Karen Davis-Bruno

Shrikant Pagay

Lily Mulugeta

Dianne Murphy

William J. Rodriguez

Maura O’Leary

Coleen LoCicero

Peter Starke

Agenda

PREA

10:30	NDA	205122	Topiramate Partial Waiver/Deferral/Plan/Appropriately Labeled	Initial monotherapy in patients ≥ 10 years of age with partial onset (POS) or primary generalized tonic- clonic (PGTC) seizures; Adjunctive therapy in patients ≥ 2 years of age with POS; Adjunctive therapy in patients ≥ 2 years of age with PGTC or seizures associated with Lennox-Gastaut syndrome (LGS)
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(b) (4)

Topiramate Partial Waiver/Deferral/Plan/Appropriately Labeled

- NDA 205122 seeks marketing approval for Topiramate for initial monotherapy in patients ≥ 10 years of age with partial onset (POS) or primary generalized tonic-clonic (PGTC) seizures; Adjunctive therapy in patients ≥ 2 years of age with POS; Adjunctive therapy in patients ≥ 2 years of age with PGTC or seizures associated with Lennox-Gastaut syndrome (LGS)
- The application has a PDUFA goal date of March 11, 2014.
- The application triggers PREA as directed to a new dosage form. The timing of this submission was before Trokendi (same indications with different age cutoffs) which is why it triggered PREA.
- *PeRC Recommendations:*

The PeRC agreed with the Division to each of the following:

- a. A partial waiver Initial Monotherapy in patients ≥ 10 years of age with partial onset or primary generalized tonic-clonic seizures.
 - i. 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):
 - ii. Deferred: 2 years up to 10 years old because labeling cannot be included until Trokendi's exclusivity has expired. However, studies cannot be conducted for monotherapy because it is now considered unethical. Therefore, labeling will be added and this PMR can be fulfilled when labeling can be added after exclusivity for Trokendi has expired.
 - iii. Appropriately labeled: 10 years up to 17 years
- b. Adjunctive therapy in patients ≥ 2 years of age with partial onset seizures
 - i. 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)
 - ii. Deferred: 1 month up to 2 years because the product is ready for approval in adults
 - iii. Appropriately labeled: 2 years to up to 17 years
- c. Adjunctive therapy in patients ≥ 2 years of age with primary generalized tonic-clonic seizures or seizures associated with Lennox-Gastaut syndrome (LGS).
 - i. 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)
 - ii. Appropriately labeled: 2 years to less than 17 years

(b) (4)

2 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

GEORGE E GREELEY
02/11/2014

MEMORANDUM of TELECONFERENCE

MEETING DATE: December 3, 2013

TIME: 4:30pm-5pm

LOCATION: CDER WO 4157 Bldg 22

APPLICATION: NDA 205122

DRUG NAME: (b) (4)

TYPE OF MEETING: Proprietary Name teleconference

MEETING CHAIRS: Lubna Merchant, DMEPA Team Leader

FDA ATTENDEES: Julie Neshiewat, PharmD, DMEPA Safety Evaluator
Ermias Zerislassie, Pharm.D, OSE Project Manager

SPONSOR ATTENDEES:

Sandra Croak-Brossman

Mark Cierpial, PhD, RAC

BACKGROUND:

On September 27, 2013, Upsher-Smith Laboratories, Inc submitted the proposed proprietary name, (b) (4) for review under NDA 205122

MEETING OBJECTIVES:

The purpose of the teleconference is to let the applicant know that DMEPA has completed a preliminary review of the proposed proprietary name, (b) (4) and finds it unacceptable because of (b) (4)

DMEPA CONCERNS WITH THE PROPOSED NAME

DMEPA has safety concerns with the proposed proprietary name, (b) (4) We reviewed the proposed proprietary name, (b) (4)

We find the name unacceptable for the following reason:

The proposed proprietary name, (b) (4)

(b) (4)

(b) (4)

Based on our assessment, we conclude (b) (4)

We recognize our conclusion differs from the conclusion in the external study conducted by (b) (4)
however, the external study did not (b) (4)

REGULATORY OPTIONS

- 1) Withdraw the proposed proprietary name, (b) (4) and submit an alternate name for our review
- 2) Wait for DMEPA to complete the review and issue a denial letter by the OSE PDUFA goal date of 12/26/13.

DISCUSSION (if any)

The Sponsor asked if the alternate name provided in the proprietary name submission, Qudexy XR, was evaluated. We stated that only a preliminary review of the alternate name, Qudexy XR, was conducted and no issues were identified. We further stated that a full review of the name, Qudexy XR, will only be conducted once a request for proprietary name review for Qudexy XR is received. The Sponsor has indicated that they will withdraw the proposed proprietary name, (b) (4) and submit an alternate name for our review.

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/s/

JULIE V NESHIEWAT
01/10/2014

Holmes, Taura

From: Holmes, Taura
Sent: Thursday, January 09, 2014 2:09 PM
To: Mark Cierpial <MCierpial@[REDACTED] (b) (4)> (MCierpial@[REDACTED] (b) (4))
Cc: Daugherty, Susan B (CSO); Ware, Jacqueline H
Subject: *NDA 205122* Information Request (Container label and Carton labeling)

Dear Mark,

I am forwarding the following recommendations from the Medication Error reviewer for NDA 205122. Please update container labels and carton labeling in accordance with these recommendations.

- A. All Container Labels and Carton Labeling (all strengths and net quantities)
1. Revise the presentation of the proprietary name from all capitals to title case in order to improve the readability of the name.
 2. We recommend choosing a more prominent color for the 'XR' in the proprietary name or consider switching the use of color in the proprietary name [REDACTED] (b) (4)
 3. Ensure that the established name has a prominence commensurate with the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
 4. Revise the statement [REDACTED] (b) (4) to read similar to "Administer dose once daily. See package insert for full prescribing information."
 5. As currently presented, there is inadequate strength differentiation within the product line. [REDACTED] (b) (4)

[REDACTED] e recommend you choose colors for the labels and labeling that are completely different from the capsule colors and adequately different from each other.

- B. Container Labels (all strengths and net quantities)
1. Increase the size and prominence of the statement "Once-Daily Dosing" by increasing the font size and moving it above the proprietary name to accommodate this revision.
 2. Decrease the font size of the "Rx only" statement and debold the statement.
 3. If space permits, relocate the "Dispense the accompanying Medication Guide to each patient" statement to beneath the strength, similar to the container labels for the 100 mg strength.

- C. Carton Labeling (all strengths and net quantities)

[REDACTED] (b) (4)

Please submit your response to this request in paper/electronic archival format as an amendment to NDA 205122. We also request that you email your response to me in advance of a formal, archival submission. Please note that both communications (both email & archive) must contain identical information.

We ask that you respond no later than the close of business January 15, 2014.

Please feel free to contact me if you should have any questions or concerns.

Kind regards,
Taura

Taura Holmes, PharmD
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I
Division of Neurology Products

Office: 301-796-1932
Fax: 301-796-9842
Email: taura.holmes@fda.hhs.gov

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/s/

TAURA N HOLMES
01/09/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205122

**PROPRIETARY NAME REQUEST
WITHDRAWN**

Upshur-Smith Laboratories, Inc.
6701 Evenstad Drive
Maple Grove, MN 55369

ATTENTION: Sandra J Croak-Brossman, PhD
Senior Director, Regulatory Affairs

Dear Dr. Croak-Brossman:

Please refer to your New Drug Application (NDA) dated and received February, 11, 2013, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Topiramate Extended-Release Capsules, 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg.

We acknowledge receipt of your correspondence, dated and received December 4, 2013, notifying us that you are withdrawing your request for a review of the proposed proprietary name (b) (4). This proposed proprietary name request is considered withdrawn as December 4, 2013.

Additionally, we acknowledge that in your correspondence, dated and received December 4, 2013, you requested a review of a new proposed proprietary name, Qudexy XR. Upon preliminary review of your submission, we have determined that it is a complete submission as described in the *Contents of a Complete Submission for the Evaluation of Proprietary Names*.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Ermias Zerislassie, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0097. For any other information regarding this application, contact Taura Holmes, Regulatory Project Manager, in the Office of New Drugs at (301) 796-1932.

Sincerely,

{See appended electronic signature page}

Ermias Zerislassie, Pharm.D., MBA, CDR USPHS
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

ERMIAS ZERISLASSIE
01/09/2014

Holmes, Taura

From: Mark Cierpial <MCierpial@ (b) (4)>
Sent: Wednesday, November 13, 2013 7:46 PM
To: Holmes, Taura
Subject: Re: *NDA 205122* Information Request

Follow Up Flag: response due
Due By: Monday, November 18, 2013 3:00 PM
Flag Status: Completed

Thank you Taura, we'll get right on it. I'll let you know if the team has any questions.

Sent from my iPad

On Nov 13, 2013, at 4:52 PM, "Holmes, Taura" <Taura.Holmes@fda.hhs.gov> wrote:

Dear Mark,

Below is a request from the Division's review team related to their ongoing review of topiramate extended release capsules.

For Study P09-003 and Study P255-103

- a. Please perform the same BE statistical analyses using a point-to-point comparison based on plasma concentrations of topiramate at each time point (Cp,t) for XR vs. IR throughout the 24-hour interval at steady state.
- b. Please provide the data for the point-to-point comparison, as described above, and the results of the BE statistical analysis for point estimates (or geometric LSM ratios) and corresponding 90% confidence intervals for comparing the plasma concentration-time curves of the two formulations. Please submit this data in both PDF and SAS .XPT format. You may also include supportive figurative illustrations for the BE results.

Please submit your response to this request in paper/electronic archival format as an amendment to NDA 205122. It would be helpful to the review team and it is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

We ask that you please respond to this request as soon as possible and no later than the close of business November 18, 2013. Please feel free to contact me if you should have any questions or concerns.

Kind regards,
Taura

Taura Holmes, PharmD
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation
Division of Neurology Products

Office: 301-796-1932

Fax: 301-796-9842

Email: taura.holmes@fda.hhs.gov



NDA 205122

INFORMATION REQUEST

Upsher-Smith Laboratories, Inc.
Attention: Cynthia G. Farner, Director, Regulatory Affairs
6701 Evenstad Drive
Maple Grove, MN 55369

Dear Ms. Farner:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Topiramate Extended-Release Capsules.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. With regard to manufacture of the product, you indicate in Module 3.2.P.3.3 that

(b) (4)

2. In accordance with 21 CFR 314.50 d(1)(ii)(c) a complete description of the commercial scale drug product manufacturing processes is required and should include all process parameters. Therefore, include a master batch record and/or a detailed manufacturing process description in section P.3.3 of the application. The Agency recognizes that changes to non-critical process parameters can usually be managed under the firm's quality system without the need for regulatory review and approval prior to implementation. However, notification of changes including changes to process parameters should be provided in accordance with 21 CFR 314.70.
3. As per 314.54(a)(1)(i), 505(b)(2) applications must provide a master batch record or a proposed master batch record. We note that you have provided executed batch records. Submit a master batch record, proposed master batch record, or confirm that the executed batch records in Module 3.2.R is identical to the master batch record for the intended commercial manufacturing process.
4. With regard to the drug product specifications, in Module 3.2.P.5.1 you designate acceptance criteria for Identification (HPLC and IR), Uniformity of Dosage Units, and (b) (4) as release specifications. It is understood that the intent is to differentiate tests that are normally only performed at product release from stability indicating tests. Confirm that the

products, if tested, will conform to all listed tests and acceptance criteria throughout shelf life.

5. You provide results for (b) (4) commercial scale batches to justify a commitment to do stability studies on the first production scale batches of the 25 mg and 200 mg product strength at each site packaged for each packaging configuration under long term conditions. This post-approval commitment for stability studies is not acceptable. We do not agree that (b) (4) commercial scale batches were represented adequately in the application data because registration stability batches of the different strengths were manufactured by (b) (4)

Therefore, the protocol needs to be revised to provide for long-term and accelerated stability data for capsule batches manufactured and packaged at full commercial scale. The post approval commitment should include a sufficient number of batches from each manufacturing site to allow for confirmation of the tentative expiration dating period assigned during the NDA review. The annual stability schedule and commitment is found to be adequate, it is the first production scale batch commitment that needs to be revised.

6. The provided dissolution data do not support the selection of your proposed acceptance criteria ranges for the 1 and 2 hour time points. Implement the following dissolution acceptance criteria for your proposed product and provide the updated specifications table for your product with the revised criteria

Acceptance criteria	
1 hr:	(b) (4)
2 hrs:	(b) (4)
6 hrs:	NLT (b) (4)

7. To support the bridge between the clinical and to-be-marketed products, provide the dissolution profiles comparisons with f2 testing in the proposed QC medium between batches produced with the clinical formulation MJ versus the commercial formulation MK.

If you have any questions, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Olen Stephens, Ph.D.
Acting Branch Chief
Branch I, Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

OLEN M STEPHENS
10/08/2013



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 205122

**PROPRIETARY NAME REQUEST
WITHDRAWN**

Upsher-Smith Laboratories, Inc.
6701 Evenstad Drive
Maple Grove, MN 55369

ATTENTION: Cynthia G. Farner
Director, Regulatory Affairs

Dear Ms. Farner:

Please refer to your New Drug Application (NDA) dated and received February 11, 2013, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Topiramate Extended-release Capsules, 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg.

We acknowledge receipt of your correspondence, dated and received on August 7, 2013, notifying us that you are withdrawing your request for a review of the proposed proprietary name (b) (4). This proposed proprietary name request is considered withdrawn as of August 7, 2013.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, a new request for a proposed proprietary name review should be submitted. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Ermias Zerislassie, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0097. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager Taura Holmes, at (301) 796-1932.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh

Director

Division of Medication Error Prevention and Analysis

Office of Medication Error Prevention and Risk Management

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
09/11/2013

MEMORANDUM of TELECONFERENCE

MEETING DATE: August 6, 2013
TIME: 11:00 am
LOCATION: CDER WO 4440 conf rm Bldg 22
APPLICATION: NDA 205122
DRUG NAME: (b) (4)
TYPE OF MEETING: Teleconference

MEETING CHAIRS: Liu Liu, DMEPA Safety Evaluator

FDA ATTENDEES: Irene Z. Chan, DMEPA Team Leader
Liu Liu, DMEPA Safety Evaluator
Jackie Shephard, DMEPA Safety Evaluator
Shawnetta Jackson, OSE SRPM

SPONSOR ATTENDEES: Cindy Farner, Director, Regulatory Affairs
Sandra Croak-Brossman, Senior Director, Regulatory Affairs
Wesley Mark Todd, Senior Director, Drug Safety and Pharmacovigilance
Greg Wedin, Associate Director, Pharmacovigilance and Risk Management
Tom Willard, Team Leader
Connie Colonnese, Project Manager

BACKGROUND:

On May 24, 2013, Upsher-Smith Laboratories, Inc submitted the proposed proprietary name, (b) (4) for review under NDA 205122.

MEETING OBJECTIVES:

The purpose of the call is to let the Applicant know that DMEPA has completed a preliminary review of the proposed name and finds it unacceptable because of (b) (4)

DMEPA CONCERNS WITH THE PROPOSED NAME

DMEPA has safety concerns with the proposed proprietary name, (b) (4) We reviewed the proposed name, considering (b) (4)

(b) (4)

(b) (4)

(b) (4)

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page.

Based on our assessment, we conclude the names (b) (4) and (b) (4) are vulnerable to name confusion that can lead to medication errors.

We recognize our conclusion differs from the conclusion in the external study conducted by (b) (4). The external study did not identify (b) (4)



REGULATORY OPTIONS

1. Withdraw the proposed name, (b) (4) and submit an alternate name for our review.
2. Wait for DMEPA to complete the review and issue a denial letter by the OSE PDUFA goal date of 8/22/13.

DISCUSSION

The Applicant questioned whether a withdrawal would stop the review clock. DMEPA confirmed that it would close the existing review clock. The submission of an alternate name would open a new review clock.

ACTION ITEMS

(DMEPA will designate final signatory authority for minutes (DMEPA TL or Deputy Director or Director)

- *Sponsor agreed to withdraw the proposed name by the end of the week.*



(b) (4)

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/s/

IRENE Z CHAN
08/21/2013



NDA 205122

INFORMATION REQUEST

Upsher-Smith Laboratories, Inc.
Attention: Cynthia G. Farner, Director, Regulatory Affairs
6701 Evenstad Drive
Maple Grove, MN 55369

Dear Ms. Farner:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Topiramate Extended-Release Capsules.

We also refer to your May 21, 2013 submission, in which you stated your plans for no longer pursuing the IVIVC for your proposed product, Topiramate Extended-Release Capsules. Therefore, the following information/data are needed to support your dissolution method and acceptance criteria. Note that in the absence of an approved IVIVC, acceptance criteria limits beyond ± 10 of the mean need to be supported by bioequivalence data.

- 1) **Dissolution Test:** Include the dissolution method report supporting the selection of the proposed dissolution test. The dissolution report should include the following information:
 - a. Solubility data for the drug substance covering the pH range;
 - b. Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (*i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.*) used to select the proposed dissolution method as the optimal test for your product. If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least ^(b)₍₄₎ % of drug release of the label amount or whenever a plateau (*i.e., no increase over 3 consecutive time-points*) is reached. We recommend use of at least twelve samples per testing variable;
 - c. Provide the complete dissolution profile data (*individual, mean, SD, profiles*) generated during the method development. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*); and
 - d. Provide data to support the discriminating capability of the proposed dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are

intentionally manufactured with meaningful variations (i.e. aberrant formulations and manufacturing conditions) for the most relevant critical manufacturing variables (e.g. drug substance particle size, compression force, tablet hardness, etc.)

In addition, if available, submit data showing the capability of the selected dissolution method to reject batches that are not bioequivalent.

- 2) **Dissolution Acceptance Criteria:** For the selection of the dissolution acceptance criterion of your product, the following points should be considered:
- a) The dissolution profile data from the pivotal clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criteria of your product (i.e., specification-sampling time point and specification value).
 - b) Specifications should be established based on average in vitro dissolution data for each lot under study, equivalent to USP Stage 2 testing (n=12).
 - c) A minimum of three time points is recommended to set the specifications. These time points should cover the early, middle, and late stages of the release profile. The last time point should be the time point where at least ^(b)₍₄₎ % of drug has release. If the maximum amount release is less than ^(b)₍₄₎ %, the last time point should be the time when the plateau of the release profile has been reached.

If you have any questions, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Acting Division Director
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAMESH K SOOD
07/19/2013



NDA 205122

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Upsher-Smith Laboratories, Inc.
Attention: Cynthia G. Farner
Director, Regulatory Affairs
6701 Evenstad Drive
Maple Grove, MN 55369

Dear Ms. Farner:

Please refer to your February 11, 2013, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Topiramate Extended-Release (ER) Capsules.

On May 21, 2013, we received your May 21, 2013, solicited major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is March 11, 2014.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by February 13, 2014.

If you have any questions, contact Taura Holmes, PharmD, Regulatory Project Manager, via email at Taura.Holmes@fda.hhs.gov or via telephone at (301) 796-1932.

Sincerely,

{See appended electronic signature page}

Russell G. Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

RUSSELL G KATZ
06/14/2013



NDA 205122

FILING COMMUNICATION

Upsher-Smith Laboratories, Inc.
Attention: Cynthia G. Farner
Director, Regulatory Affairs
6701 Evenstad Drive
Maple Grove, MN 55369

Dear Ms. Farner:

We acknowledge receipt of your New Drug Application (NDA) dated February 11, 2013, received February 11, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Topiramate Extended-Release (ER) Capsules.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is December 11, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by November 13, 2013.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

REQUESTS FOR ADDITIONAL INFORMATION

We request that you submit the following information:

1. In reference to your March 15, 2013, email proposal for the submission of the study P09-004 safety results, we agree with your proposal to submit the study as a 120-day safety update to the ISS. The resulting safety update ISS should contain an integrated narrative discussion of the phase 1 safety results along with the study P09-004 safety results and appropriate supporting tables. An ISS comprised of tables alone is not acceptable. We also request that you submit the study P09-004 safety datasets as SAS transport files (.xpt) and include the adverse event, vital sign, ECG, concomitant medication, demographic, treatment assignment, laboratory and other safety related datasets.
2. In addition to the aforementioned safety data, please provide top line efficacy results for study P09-004 when available. This submission should include summary tables describing the primary and any available secondary endpoint analysis results with p values. Please include the protocol and analysis plan. Datasets are not required.
3. Please submit the dissolution method report supporting the proposed QC/IVIVC dissolution method.
4. We note that the *In Vitro in Vivo* Correlation (IVIVC) was (b) (4)
[REDACTED]
[REDACTED] This information should be submitted to the NDA as soon as it is available.
5. Please submit the (b) (4) used in the construction of the IVIVC in SAS transport tabulated format.
6. Please submit the mean dissolution profiles used in the construction of the model in SAS transport tabulated format.
7. Please submit all the input and output files generated during the development and validation of the IVIVC model.
8. Please note that (b) (4) should be based on IVIVC predictions. (b) (4)
[REDACTED]
[REDACTED]
9. The IVIVC model was constructed (b) (4)
[REDACTED]
[REDACTED]
10. Please provide the electronic datasets that were used in the: (1) supportive meta-analysis

for the (b) (4) and the (2) supportive analyses (i.e., Topiramate IR Shape Simulation Report and Steepness of Concentration-Response Simulation Reports) in Module 5.3.6 Reports of Postmarketing Experience.

11. Please provide the Data Definition files for all the clinical pharmacology and biopharmaceutics studies in PDF format.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

LABELING

We acknowledge your request for a waiver of the requirement that the **Highlights** of Prescribing Information be limited to no more than one-half page. We will consider your request during labeling discussions.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the

product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Neurology Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

(b) (4)



SUBMISSIONS AND COMMUNICATIONS

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products (DNP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please contact Taura Holmes, PharmD, Regulatory Project Manager, via email at taura.holmes@fda.hhs.gov or via telephone at (301) 796-1932.

Sincerely,

{See appended electronic signature page}

Russell G. Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

RUSSELL G KATZ
04/26/2013

**CERTIFICATION: FINANCIAL INTERESTS AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

TO BE COMPLETED BY APPLICANT

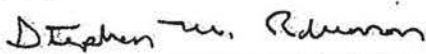
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- ☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See attached list of clinical investigators.	

- ☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- ☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME: Stephen M. Robinson	TITLE: Chief Financial Officer & Executive Vice President
FIRM/ORGANIZATION: Upsher-Smith Laboratories, Inc.	
SIGNATURE: 	DATE (mm/dd/yyyy): 01/22/2013

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right.

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, 420A
Rockville, MD 20850

Upsher-Smith Laboratories, Inc.
Original New Drug Application/NDA 205122
Topiramate Extended Release Capsules

FINANCIAL CERTIFICATION AND DISCLOSURE

Attachment to Form FDA 3454: List of Clinical Investigators for Covered Studies

Clinical Studies P09-001, P09-002, and P09-003

Aziz L. Laurent, M.D., Principal Investigator for P09-001 and P09-002

Ikenna Ogbaa, M.D., Principal Investigator for P09-003

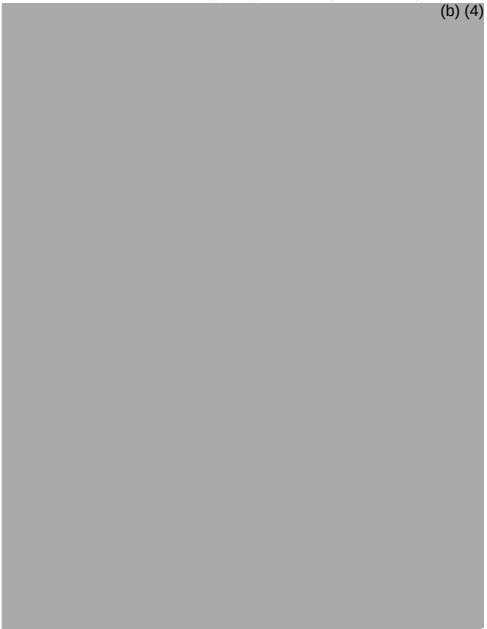
(b) (4)

A large rectangular area of the document is redacted with a solid gray fill, covering the names and affiliations of the clinical investigators for studies P09-001, P09-002, and P09-003.

Clinical Study P09-011

Robert I. Cooper, M.D., Principal Investigator for P09-011

(b) (4)

A large rectangular area of the document is redacted with a solid gray fill, covering the names and affiliations of the clinical investigators for study P09-011.

FINANCIAL CERTIFICATION AND DISCLOSURE

Attachment to Form FDA 3454: List of Clinical Investigators, Continued

Clinical Studies P255-101 and P255-102

Mark T. Leibowitz, M.D., Principal Investigator for P255-101 and P255-102

(b) (4)



Clinical Study P255-103

Mark J. Allison, M.D., CPI, Principal Investigator for P255-103

(b) (4)





DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 69,257

MEETING MINUTES

Upsher-Smith Laboratories, Inc.
Attention: Sandra Croak-Brossman, PhD
Sr. Director, Regulatory Affairs
6701 Evenstad Drive
Maple Grove, MN 55369-6026

Dear Dr. Croak-Brossman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for USL255 (topiramate extended-release) capsules.

We also refer to the meeting between representatives of your firm and the FDA on October 31, 2012. The purpose of the meeting was to discuss your meeting package for epilepsy.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1056.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A
Meeting Category: Advice

Meeting Date: October 31, 2012
Meeting Location: FDA White Oak

Application Number: IND 69,257
Product Name: USL255 (topiramate extended-release) capsules
Indication: Epilepsy
Sponsor/Applicant Name: Upsher-Smith Laboratories (USL)

FDA ATTENDEES

Russell Katz, MD, Division Director, Division of Neurology Products (DNP)
Norman Hershkowitz, MD, Deputy Director, DNP
Steven Dinsmore, MD, Clinical Reviewer, DNP
Angela Men, PhD, Acting Clinical Pharmacology Team Leader
Ta-Chen Wu, PhD, Clinical Pharmacology Reviewer
Kalah Auchincloss, JD, MPH, Regulatory Counsel, Office of Regulatory Policy (ORP)
Michael Bernstein, JD, Regulatory Counsel, ORP
Lana Chen, RPh, Project Manager, DNP

SPONSOR ATTENDEES

Mark Cierpial, PhD, RAC, USL255 Regulatory Lead
Sandra Croak-Brossman, PhD Regulatory Affairs, Senior Director
Annie Clark, PharmD, PhD Clinical Development, Clinical Research Scientist
Dave Townson, PhD, PMP, Project Leader, CNS

Via telephone conference:

William Pullman, MB, BS, PhD, FRACP, Chief Scientific Officer
W. Mark Todd, MD, Senior Director, Drug Safety & Pharmacovigilance & Chief Safety Officer
Bob Anders, PharmD, Director, Clinical Development
Cindy Farner, RAC, Director, Regulatory Affairs

Question #1: Upsher-Smith intends to file a 505(b)(2) NDA for USL255 based on PK data from the clinical pharmacology studies (described in Sections 4 and 9 of the Briefing Document) and appropriate analyses of partial AUC (described in Section 5 of the Briefing Document). The NDA will also include predicted clinical response for monotherapy and adjunctive treatment of partial-onset and primary generalized tonic-clonic seizures derived from the validated Topamax PK-PD models. Further, the NDA will provide a rationale detailing why the differences in t_{max} and/or shape of the plasma concentration-time profile between Topamax and USL255 will not have a significant effect on clinical efficacy. Subject to data review, does the Agency agree that this approach would be sufficient to support approval of USL255 for the following indications?

- Initial monotherapy for patients with partial onset or primary generalized tonic-clonic seizures
- Adjunctive therapy for patients with partial onset or primary generalized tonic-clonic seizures
- Adjunctive therapy for patients with seizures associated with Lennox-Gastaut syndrome

Question #2: Does the overall package of studies, as outlined in Section 9 of the Briefing Document, provide adequate support for filing and ultimate approval of USL255 for the stated indications?

Preliminary FDA Response to Questions #1 and #2 :

We believe the strongest argument is your partial AUC analysis. We continue to have a concern, however, about the possibility that an extended release topiramate product whose concentration-time curve does not closely match that of the innovator product might differ in effect from the innovator product. We thus urge you to consider whether there may be additional data or arguments that you may present to address that concern with respect to your proposed product. Your other mechanistic arguments around this issue are helpful but alone are not sufficient for approval.

We cannot say at this point whether your proposal would support approval. We believe, however, that the application is fileable.

ADDITIONAL COMMENTS

Additional recommendations and information on the submission of an application through the 505(b)(2) regulatory pathway

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its

October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate. We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature.

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

Information in your meeting briefing document suggests that you are proposing to reference information from FDA reviewers' public summaries for support of safety and/or efficacy. This is not acceptable. We note that a 505(b)(2) applicant that seeks to rely upon the Agency's finding of safety and/or effectiveness for a listed drug, may rely only on that finding as is reflected in the approved labeling for the listed drug.

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of

administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Since your product is a new dosage form, you will need to submit a Pediatric Study Plan.

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a Pediatric Study Plan, and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes.

Follow-up Questions to FDA Preliminary Comments:

1. You stated in your preliminary comments that you viewed our partial AUC analysis to be the strongest argument. We'd like to understand if it's possible to gain approval for an extended-release product like USL255 based solely on an analysis of partial AUC, and if so, what specific results would need to be obtained? For example, what specific time intervals would need to be evaluated? Would the analysis need to show equivalence at each of these time intervals?

Meeting Discussion:

The Sponsor noted that they are interested in submitting a 505(b)(2) application as soon as possible and they would like a rapid review of the application.

The Sponsor inquired as to what we thought about the AUC argument. The Division responded that this was an important and useful argument, but the Sponsor should consider further the issue of comparing plasma concentration curves.

The sponsor proposed further exploration of partial AUC, such as increasing the number of partial intervals; however the overall conclusion of this discussion was that no further expansion of the partial AUC methodology was necessary.

2. As discussed in Section 6 of our Briefing Document, a PK-PD model has been developed and published for topiramate that identified C_{min} as the PK parameter related to clinical efficacy in both the monotherapy and adjunctive treatment settings. The steady-state PK study P09-003 demonstrated that USL255 maintains an equivalent C_{min} , the PK parameter related to efficacy, compared to Topamax. Given the PK-PD relationship, USL believes that maintenance of C_{min} with an extended-release topiramate will provide similar clinical efficacy demonstrated by the innovator drug (Topamax). Does the Agency agree that the PK-PD relationship established for Topamax can be used for the approval of an extended-release product such as USL255?

Meeting Discussion: Although maintenance of C_{min} is supportive, this data along with the concentration response argument with or without partial AUC argument may not be sufficient to achieve approval.

3. Does the Agency have any specific recommendations for additional data or information that would address its concern regarding *an extended-release topiramate product whose concentration-time curve does not closely match that of the innovator product?*

Meeting Discussion: There was lengthy discussion surrounding this question but the overall conclusion is the division cannot provide specifics on a path forward. The division did indicate the application as proposed does not address all concerns in full, but is reviewable. FDA is obliged to keep confidential arguments and information submitted by other applicants. FDA has stated the concerns as clearly as possible, and encourages the Sponsor to keep those concerns in mind as their position is formulated. FDA will not, however, be able to provide any recommendations concerning arguments, data, or information to address our concerns that have not been proposed by the Sponsor.

4. Regarding the Pediatric Study Plan for USL255, we plan to request labeling for the indications listed in our Briefing Package (b) (4)

Does the Agency agree with this approach?

Meeting Discussion:

(b) (4)

Refer to the previous FDA comment under Additional Comments/Pediatrics. Since your product is a new dosage form, you will need to submit a Pediatric Study Plan for review.

Additional discussion:

The sponsor pursued discussion of submission options which may be available to achieve the earliest approval possible. Since approval based on PK data alone is not a certainty, the sponsor indicated clinical trial results in support of efficacy will be available for submission in the second quarter of next year. The sponsor questions if a complete NDA 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 is an unsatisfactory proposal because a clinical trial would not be a minor amendment. Submission of a clinical trial would extend the review clock an additional three months, so unless the amendment was submitted soon after the PK package this method would not advance the approval date. (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

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/s/

RUSSELL G KATZ

11/30/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 69,257

MEETING PRELIMINARY COMMENTS

Upsher-Smith Laboratories, Inc.
Attention: Sandra Croak-Brossman, PhD
Sr. Director, Regulatory Affairs
6701 Evenstad Drive
Maple Grove, MN 55369-6026

Dear Dr. Croak-Brossman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for USL255 (topiramate extended-release) capsules.

We also refer to your August 14, 2012, correspondence, received August 14, 2012, requesting a meeting to discuss your Type A meeting package for epilepsy.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-1056.

Sincerely,

{See appended electronic signature page}

Lana Chen, RPh
Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

PRELIMINARY MEETING COMMENTS

Meeting Type: Type A
Meeting Category: Advice
Meeting Date: October 30, 2012
Meeting Location: FDA White Oak
Application Number: IND 69,257
Product Name: USL255 (topiramate extended-release) capsules
Indication: Epilepsy
Sponsor/Applicant Name: Upsher-Smith Laboratories (USL)

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for October 30, 2012, between USL and the Division of Neurology. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

1.0 DISCUSSION

Question #1: Upsher-Smith intends to file a 505(b)(2) NDA for USL255 based on PK data from the clinical pharmacology studies (described in Sections 4 and 9 of the Briefing Document) and appropriate analyses of partial AUC (described in Section 5 of the Briefing Document). The NDA will also include predicted clinical response for monotherapy and adjunctive treatment of partial onset and primary generalized tonic-clonic seizures derived from the validated Topamax PK-PD models. Further, the NDA will provide a rationale detailing why the differences in tmax

and/or shape of the plasma concentration-time profile between Topamax and USL255 will not have a significant effect on clinical efficacy. Subject to data review, does the Agency agree that this approach would be sufficient to support approval of USL255 for the following indications?

- Initial monotherapy for patients with partial onset or primary generalized tonic-clonic seizures
- Adjunctive therapy for patients with partial onset or primary generalized tonic-clonic seizures
- Adjunctive therapy for patients with seizures associated with Lennox-Gastaut syndrome

Question #2: Does the overall package of studies, as outlined in Section 9 of the Briefing Document, provide adequate support for filing and ultimate approval of USL255 for the stated indications?

Preliminary FDA Response to Questions #1 and #2 :

We believe the strongest argument is your partial AUC analysis. We continue to have a concern, however, about the possibility that an extended release topiramate product whose concentration-time curve does not closely match that of the innovator product might differ in effect from the innovator product. We thus urge you to consider whether there may be additional data or arguments that you may present to address that concern with respect to your proposed product. Your other mechanistic arguments around this issue are helpful but alone are not sufficient for approval.

We cannot say at this point whether your proposal would support approval. We believe, however, that the application is fileable.

ADDITIONAL COMMENTS:

Additional recommendations and information on the submission of an application through the 505(b)(2) regulatory pathway

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

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If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate. We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature.

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

Information in your meeting briefing document suggests that you are proposing to reference information from FDA reviewers' public summaries for support of safety and/or efficacy. This is not acceptable. We note that a 505(b)(2) applicant that seeks to rely upon the Agency's finding of safety and/or effectiveness for a listed drug, may rely only on that finding as is reflected in the approved labeling for the listed drug.

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived,

deferred, or inapplicable. Since your product is a new dosage form, you will need to submit a Pediatric Study Plan.

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a Pediatric Study Plan, and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes.

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/s/

LANA Y CHEN

10/26/2012



IND 069257

ADVICE/INFORMATION REQUEST

Upsher-Smith Laboratories, Inc.
Attention: Cynthia G. Farner
Director, Regulatory Affairs
6701 Evenstad Drive,
Maple Grove, MN 55369-6026

Dear Ms. Farner:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Topiramate extended-release oral formulation (USL255).

We also refer to your following amendments:

Serial No.	Submitted on:	Containing:
039	Jul 18, 2011	Briefing package with a summary of available data regarding thorough QTc and alcohol interaction information related to USL255.
041	Aug 26, 2011	Request for a waiver of thorough QT data requirements, (b) (4)
046	Oct 28, 2011	Request for FDA feedback on the draft Blinded Data Review (BDR) plan for Study P09-004.

We have the following comments:

Thorough QT Safety Requirements

USL Question: Does the Agency agree that the data package adequately establishes the cardiac conduction safety of topiramate and that no further cardiac safety data are required to support approval of USL255?

FDA response:

Yes. We agree that no further QT assessment is needed for topiramate extended-release (USL255) formulation.

Alcohol Interaction Safety Requirements

USL Question: USL understands that final labeling content is a review issue;

(b) (4)

FDA response:

As noted in our Type C meeting minutes dated 8/24/11, we recommend that you generate appropriate *in vitro* data first. Once appropriate *in vitro* data are generated, depending upon the results, you then can propose whether an *in vivo* study is needed. Alternatively, you could propose labeling with adequate justification, and we will entertain further discussion at that point.

Blinded Data Review Plan

USL Question: The purpose of this submission is to request FDA feedback on the attached Draft BDR Plan. Specifically, are the methods and procedures outlined in the plan acceptable to the Agency? The main objective of the BDR is to re-assess the sample size needed for the primary efficacy comparison in the trial.

FDA response:

This submission (Serial No. 46) includes a draft blinded data review (BDR) plan for study P09-004. The BDR plan appears acceptable. We do not have any additional comments.

If you have any questions, please contact Lana Chen, Senior Regulatory Project Manager, by phone (301) 796-1056 or email: Lana.Chen@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Russell G. Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

RUSSELL G KATZ
07/16/2012



IND 69,257

MEETING MINUTES

Upsher-Smith Laboratories, Inc.
Attention: Cynthia G. Farner, RAC
Director, Regulatory Affairs
6701 Evenstad Drive
Maple Gtove, MN 55369-6026

Dear Ms. Farner:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Topiramate Extended-Release Capsules.

We also refer to the meeting between representatives of your firm and the FDA on July 27, 2010. The purpose of the meeting was to following:

- Adequacy of proposed dissolution profile evaluation approach to support commercial specification development.
- Adequacy of proposed approach to providing comparative dissolution profiles in lieu of bioequivalence or other in vivo bridging study data to support changes during development and the intended commercial drug product.
- Adequacy of proposed dissolution methodology and data to demonstrate product performance in alcoholic media.
- Adequacy of proposed stability data to support the NDA submission and commercial product.
- Adequacy of the proposed plan to support the addition of a 150 mg capsule strength in the NDA.
- Adequacy of the proposed plan to support the addition of an alternate manufacturing site in the NDA.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Teshara G. Bouie, MSA, OTR/L

CDR, USPHS, Regulatory Health Project Manager
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Guidance

Meeting Date and Time: July 27, 2011
Meeting Location: White Oak Building 22, Conference Room: 1417

Application Number: IND 69,257
Product Name: Topiramate Extended-Release Capsules
Indication: Seizures
Sponsor/Applicant Name: Upsher-Smith Laboratories, Inc.

Meeting Chair: Ramesh Sood
Meeting Recorder: Teshara G. Bouie

FDA ATTENDEES

Office of New Drug Quality Assessment

Ramesh Sood, Ph.D., Branch Chief
Thomas Wong, Ph.D., CMC Reviewer
John Duan, Ph.D., Biopharmaceutics Reviewer
Teshara G. Bouie, Regulatory Health Project Manager

Office of Clinical Pharmacology

Ta-Chen Wu, Ph.D., Clinical Pharmacologist

SPONSOR ATTENDEES

Beth A-S. Brown, Ph.D., R.Ph., Director, Pharmaceutical Development
Jaidev S. Tantry, Ph.D., Principal Scientist, Pharmaceutical Development
Mark Heintz, Ph.D., Principal Chemist, Chemistry and Analytical Sciences
Lawrence Lambrecht, Pharm.D., Clinical Project Manager, Clinical Development
Margarita Aguilera, Senior Director, Regulatory Affairs
Cynthia Farner, RAC, Director, Regulatory Affairs
Wesley Mark Todd, M.D., Senior Director, Medical Affairs (Program Leader)

1.0 BACKGROUND

IND 69,257 is indicated for initial monotherapy and/or adjunctive therapy for patients with partial onset or primary generalized tonic-clonic seizures, and adjunctive therapy for patients with seizures associated with Lennox-Gastaut syndrome.

On April 29, 2011, the sponsor requested a meeting to discuss data requirements for certain CMC aspects of the USL255 drug development program, future NDA submission and commercialization.

2. DISCUSSION

Dissolution Questions

Question 1:

Does the Agency agree that no additional in vivo clinical data are needed to bridge the MD Phase 1 PK data, the MJ Phase 3 efficacy data and the MK proposed commercial product?

FDA Preliminary Response:

Additional bioavailability studies are needed based on the following considerations.

- *There is no bioavailability information available from MJ or MK formulation*
- *The MD formulation was used in Phase 1 studies to provide PK information and support the selection for dosing regiment, but was not studied in any of the efficacy studies.*
- *There are significant differences between MJ (or MR) formulation and MD formulation.*

Therefore, the following studies are recommended.

- *A steady state study characterizing the bioavailability of the to-be-marketed formulation comparing to the immediately release formulation regarding the concentration fluctuation index (peak to trough ratio).*
- *A food effect study using the to-be-marketed formulation.*

Meeting Discussion:

The Sponsor reiterated that the difference in coating weight between MD and MJ (or MK) falls into Level-3 difference. However, the color change is the major difference between MJ and MK formulations, and thus any bridging study should not be necessary. The Agency agreed.

The Sponsor sought the acceptance for conducting a single-dose BE study to bridge the MD and MJ/MK formulation. The Agency reiterated the CFR requirement for the need to characterize and differentiate the concentration-time profiles between the extended-release drug formulation and the immediate-release drug product at steady-state, in particular the peak, trough and the fluctuation of the profile, especially when PK profile of MJ or MK has not been characterized. The Agency mentioned that the effect of food can be evaluated in a single-dose study; not necessarily at the steady-state in the repeat-dose study.

The Sponsor sought clarification on whether it is necessary to compare MJ with the reference IR formulation, in addition to MD vs. MJ, at steady-state. The Agency clarified that MD formulation has been demonstrated to be bioequivalent to the reference IR; therefore, it is necessary to link the MD to the MJ or MK formulation, but not necessarily to compare with the IR again. The steady-state evaluation can be conducted with the highest strength of ER formulation. After the establishment of BE, the linkage for the lower strengths can be established via biowaiver, depending on the formulations. The Sponsor indicated that formulations across the strengths are the same.

The sponsor mentioned that they are planning to conduct a PK/PD study, comparing MJ and IR formulations at steady-state. In this planned study, cognitive function will be the primary endpoint, whereas PK will be a secondary endpoint. The duration of the study will be 45 days. Food intake will be expected during the study. The Sponsor sought the Agency's feedback on (1) whether the PK results from this PK/PD study can be used to supplement the BE evaluation, and (2) whether it is still necessary to examine MD vs. MK in this study, and the PK parameters of interest at steady-state. The Agency responded that this proposed study can be modified to substitute the above mentioned study to characterize the steady state bioavailability (including C_{max}, C_{min}, and AUC), and the fluctuation index. The inclusion of MD formulation in this study is not necessary. Further, it will be helpful to document the food intake and timing in this study to provide supporting information with respect to the potential effect of food on the release characteristics of the proposed to-be-marketed ER formulation.

Question 2:

Does the Agency agree that the proposed approach to develop dissolution specifications for inclusion in the NDA is acceptable?

FDA Preliminary Response:

1. You are reminded that the current dissolution acceptance (b) (4) % at 3 hours is not adequate.
2. It is not clear what the definition of mean dissolution profile is. In general practice, at least 6 dosage units should be tested. Both the mean and the individual values should be taken into consideration based on USP <711> Table 2. In addition to the mean values, the standard deviations and/or coefficient of variation (CV) should also be provided.
3. Although the in vitro release specification with three points may be adequate, the acceptance criteria at each time point should be set based on the data. The MD formulation did not show similarity with MJ formulation with an f₂ value of 47.86 (only one time point with value more than (b) (4) % was used for calculation). Therefore, it is not appropriate to take MD formulation into consideration when the acceptance criteria are set.
4. Based on the limited data provided, it is not reasonable to widen the acceptance criterion at 2 hours to the range of (b) (4) % where MD formulation was taken into consideration.

Meeting Discussion:

The Agency clarified that when setting the dissolution acceptance criteria, the mean dissolution data in each batch should be considered in addition to the values of the individual units. The sponsor stated that there was considerable variability in the dissolution data and expressed the intention to provide a justification using the in vivo data to explore the possibility of expanding the range of the acceptance criteria. The Agency mentioned that the use of such approach would allow for the setting of more clinically relevant dissolution acceptance criteria.

Question 3:

Does the Agency agree that the proposed in vitro alcoholic dissolution data and methodology are adequate to characterize the extended-release product performance in the presence of alcohol?

FDA Preliminary Response:

The in vitro dose-dumping study using the intact drug product in acidic alcohol media at pH 1.2 should be conducted because it represents a more physiologically relevant condition.

Based on the preliminary in vitro data provided, there is a potential for alcohol related dose dumping. If the final dissolution results are similar to the preliminary results you presented, you then should consider performing an in vivo alcohol interaction study.

Meeting Discussion:

[REDACTED] (b) (4)

The Agency disagreed and retained their original recommendation. In addition, the Agency recommended that the Sponsor conduct with the drug product an in vitro alcohol dose dumping dissolution study using different concentrations of alcohol at pH 1.2, pH 4.5 and pH 6.8. The pH 6.8 dissolution medium could be substituted by the current medium at pH 7.2,. The Sponsor agreed with the Agency's recommendation but stated that even at pH 4.5 the variability would be greater because of the salt content in the lower pH dissolution media.

Stability Questions

Question 1:

Does the Agency agree that the planned stability studies are adequate to support the proposed commercial MK formulation in bottle counts between 30 and 500 capsules per bottle containing desiccant in canisters or packets, and the unit dose container closure configuration, with a minimum 24 month shelf life, assuming acceptable data?

FDA Preliminary Response:

Your planned stability studies are adequate to support the proposed commercial MK formulation in all of the proposed packaging configurations. A final decision on the shelf-life of the product will be made as part of the NDA review based on the data submitted.

Meeting Discussion:

No further discussion at the meeting.

Question 2:

Does the Agency agree that the proposed addition of an intermediate 150 mg strength for the commercial product (MK formulation), with the same expiry period as the other strengths, is acceptable without providing additional stability data in the NDA?

FDA Preliminary Response:

It is acceptable to grant the same expiry period as the other strength capsules to the 150 mg strength capsule without providing additional stability data in the NDA. Include your rationale in the NDA.

Meeting Discussion:

No further discussion at the meeting.

Alternate Manufacturing Site Questions

Question 1:

Does the Agency agree that the planned approach with batch release data for one batch, and comparative dissolution profiles and stability studies for each capsule strength, are adequate to support the proposed addition of an alternate manufacturing site, assuming acceptable data?

FDA Preliminary Response:

Your proposed planned approach of providing batch release data for one batch and stability studies for each capsule strength is insufficient to support the proposed addition of an alternate manufacturing site. As the alternate manufacturing site is located in another state, it is considered as Level 3 change according to the SUPAC-MR Guidance. Since you don't have significant body of information on the product, considering the principles described in the SUPAC-MR Guidance you need to provide three batches of each capsule strength manufactured at the proposed alternate manufacturing site with three months' accelerated stability data in the NDA submission in order to support the proposed alternate manufacturing site. You may use bracketing approach, if applicable, for your stability program.

A bioequivalence study is required for the new site.

Meeting Discussion:

The sponsor agreed that their bracketing design will include the 25 mg and 200 mg strengths in 30 and 500 count bottles and unit dose for all strengths. The sponsor would also provide 3 months of stability data on 3 batches.

Question 2:

Does the Agency agree that no additional in vivo clinical data are needed to support the alternate manufacturing site for this extended-release drug product?

FDA Preliminary Response:

No. A bioequivalence study is required for the new site.

Meeting Discussion:

No further discussion at the meeting.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

4.0 ACTION ITEMS

None.

{See appended electronic signature page}

Teshara G. Bouie
Regulatory Health Project Manager
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Branch I, Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

TESHARA G BOUIE
08/24/2011

RAMESH K SOOD
08/24/2011