

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205122Orig1s000

OTHER REVIEW(S)

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 205122 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Qudexy XR Established/Proper Name: topiramate extended-release Dosage Form: capsules Strengths: 25 mg, 50 mg, 100 mg, 150 mg, 200 mg		
Applicant: Upsher-Smith Laboratories Inc. (USL) Agent for Applicant (if applicable):		
Date of Application: February 11, 2013 Date of Receipt: February 11, 2013 Date clock started after UN:		
PDUFA Goal Date: March 11, 2014	Action Goal Date (if different):	
Filing Date: April 26, 2013	Date of Filing Meeting: April 9, 2013	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Class 3 (new dosage form)		
Proposed indication(s)/Proposed change(s): <ul style="list-style-type: none"> ▪ 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 partial onset seizures or primary generalized tonic-clonic seizures, and seizures associated with Lennox-Gastaut syndrome (LGS) <p style="margin-left: 20px;">[Note: These are the same epilepsy indications as approved for Topamax, except Topamax is indicated for a lower age range (i.e., ≥ 2 years of age) in initial monotherapy. The lower age range is protected by Hatch-Waxman exclusivity until July 15, 2014, and is appropriately carved out of the USL topiramate extended-release capsules labeling.</p> <p style="margin-left: 20px;">Topamax is also approved for the treatment of migraine. The applicant is not seeking this indication.]</p>		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.</i>		
Type of BLA <i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package	

<p><i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i></p>	<ul style="list-style-type: none"><input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.)<input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.)<input type="checkbox"/> Device coated/impregnated/combined with drug<input type="checkbox"/> Device coated/impregnated/combined with biologic<input type="checkbox"/> Separate products requiring cross-labeling<input type="checkbox"/> Drug/Biologic<input type="checkbox"/> Possible combination based on cross-labeling of separate products<input type="checkbox"/> Other (drug/device/biological product)
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<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): 69257				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

User Fee Status <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>		Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>		Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
505(b)(2) (NDAs/NDA Efficacy Supplements only)		YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	This application is a duplicate; however, it was submitted before the approval of the listed drug (Troken [®] XR)
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	This application provides for an extended release dosage form than the RLD (immediate release topiramate); however, it is a duplicate of an approved application (Troken [®] XR)
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i>					
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm					
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code		Exclusivity Expiration	
NDA 20505	Topiramate [®] Tablets	NPP		July 15, 2014	

NDA 20844	Topamax [®] Sprinkle Capsules	NPP	July 15, 2014	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>				
Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: (b) (4)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p>Index: Does the submission contain an accurate comprehensive index?</p>	<input type="checkbox"/>	<input type="checkbox"/>		
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain.</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p>BLAs only: Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Forms and Certifications				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p>				
Application Form	YES	NO	NA	Comment
<p>Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?</p> <p><i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<i>314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] 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." Applicant may not use wording such as, "To the best of my knowledge..."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?</p> <p><i>If no, request in 74-day letter</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
<p>Is a proposed proprietary name submitted?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	QT Interdisciplinary Review Team (sent 01/16/14)
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 9, 2013

BLA/NDA/Supp #: 205122

PROPRIETARY NAME: Qudexy XR

ESTABLISHED/PROPER NAME: topiramate extended-release

DOSAGE FORM/STRENGTH: capsules (25 mg, 50 mg, 100 mg, 150 mg, 200 mg)

APPLICANT: Upsher-Smith Laboratories, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

- 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 partial onset seizures or primary generalized tonic-clonic seizures, and seizures associated with Lennox-Gastaut syndrome (LGS)

BACKGROUND: These are the same epilepsy indications as approved for Topamax, except Topamax is indicated for a lower age range (i.e., ≥ 2 years of age) in initial monotherapy. The lower age range is protected by Hatch-Waxman exclusivity until July 15, 2014, and is appropriately carved out of the USL topiramate extended-release capsules labeling.

Topamax is also approved for the treatment of migraine. The applicant is not seeking this indication.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Taura Holmes	Y
	CPMS/TL:	Jacqueline Ware	N
Cross-Discipline Team Leader (CDTL)	Norman Hershkowitz		Y
Clinical	Reviewer:	Steven Dinsmore	Y
	TL:	Norman Hershkowitz	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		

Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		
	Reviewer:	Ta-Chen Wu	Y
	TL:	Yuxin Men	Y
Biostatistics	Reviewer:	Ohidul Siddiqui	Y
	TL:	Kun Jin	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Edward Fisher	N
	TL:	Lois Freed	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Charles Jewell Biopharmaceutics: Deepika Lakhani Sandra Suarez	Y N Y
	TL:	Martha Heimann Biopharmaceutics: Angelica Dorantes	Y N
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Xingfang Li Michael F. Skelly	N N
	TL:	Sam H. Haider William H. Taylor	N N
OSE/DMEPA (proprietary name)	Reviewer:	Jacqueline Sheppard	N
	TL:	Julie Neshiewat	Y
OSE/DRISK (REMS)	Reviewer:		
	TL:		

OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Twanda Scales (PLT) Aline Moukhtara (OPDP)		N N
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>For formulation bridging, studies P09-003 and 255-103 were conducted, both including steady-state PK and BA/BE comparing the proposed drug products with the reference listed drug Topamax immediate-release tablets.</p>
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<p><input type="checkbox"/> Not Applicable</p>

<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain: PK studies were completed in support of approval</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

Comments:	<input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
BIOSTATISTICS	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only)	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
<u>Environmental Assessment</u>	
<ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
If no , was a complete EA submitted?	<input type="checkbox"/> YES <input type="checkbox"/> NO
If EA submitted , consulted to EA officer (OPS)?	<input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
<u>Quality Microbiology (for sterile products)</u>	<input checked="" type="checkbox"/> Not Applicable
<ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) 	<input type="checkbox"/> YES <input type="checkbox"/> NO

Comments:	
<u>Facility Inspection</u> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<u>Facility/Microbiology Review (BLAs only)</u> Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<u>CMC Labeling Review</u> Comments:	<input type="checkbox"/> Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input checked="" type="checkbox"/> N/A <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	

<ul style="list-style-type: none"> Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Eric Bastings, MD, Deputy Director

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V):

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>

ACTIONS ITEMS

<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product

	Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

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
03/11/2014

505(b)(2) ASSESSMENT

Application Information		
NDA # 205122	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Qudexy XR Established/Proper Name: topiramate Dosage Form: extended-release capsules Strengths: 25 mg, 50 mg, 100 mg, 150 mg, 200 mg		
Applicant: Upsher-Smith Laboratories Inc. (USL)		
Date of Receipt: February 11, 2013		
PDUFA Goal Date: March 11, 2014		Action Goal Date (if different):
RPM: Taura Holmes, PharmD		
Proposed Indication(s): <ul style="list-style-type: none"> ▪ 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 partial onset seizures or primary generalized tonic-clonic seizures, and seizures associated with Lennox-Gastaut syndrome (LGS) <p style="margin-top: 10px;">[Note: These are the same epilepsy indications as approved for Topamax, except Topamax is indicated for a lower age range (i.e., ≥2 years of age) in initial monotherapy. The lower age range is protected by Hatch-Waxman exclusivity until July 15, 2014, and is appropriately carved out of the USL topiramate extended-release capsules labeling.</p> <p style="margin-top: 10px;">Topamax is also approved for the treatment of migraine. The applicant is not seeking this indication.]</p>		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?
- YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Topamax package insert NDA 20844 (Topamax [®] Sprinkle Capsules) NDA 20505 (Topamax [®] Tablets)	Non-clinical
Topamax package insert NDA 20844 (Topamax [®] Sprinkle Capsules) NDA 20505 (Topamax [®] Tablets)	Safety and efficacy

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The application contains CMC information and clinical pharmacology studies. A brief description of the bridging studies (Study P09-003 and Study 255-103) is listed below:

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

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If “NO,” proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4(c).

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?
 YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?
 YES NO
If "NO," proceed to question #10.

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Topamax (topiramate) Tablets	20505	Y
Topamax (topiramate) Sprinkle Capsules	20844	N

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?
 N/A YES NO
If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

8) Were any of the listed drug(s) relied upon for this application:
 a) Approved in a 505(b)(2) application?
 YES NO
If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?
 YES NO
If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?
 YES NO

If “**YES**”, please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES NO

If “**YES**”, please list which drug(s) and answer question d) i. below.

If “**NO**”, proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

This application provides for a new extended-release dosage form. The RLDs are immediate-release products.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

*If "NO" to (a) proceed to question #11.
If "YES" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A YES NO

*If this application relies only on non product-specific published literature, answer "N/A"
If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO
If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO
See below for explanation.

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A YES NO
See below for explanation.

*If this application relies only on non product-specific published literature, answer "N/A"
If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): [Trokendi XR Capsules \(NDA 201635\)](#) and [Topamax Sprinkle Capsules \(NDA 20844\)](#) are pharmaceutical alternatives to USL's topiramate capsules.

[In addition, the numerous generic pharmaceutical alternatives \(topiramate immediate-release generic tablets and generic capsules\) are not RLDs.](#)

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): [List is attached](#)

No patents listed proceed to question #14

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s): [7,125,560; see attached list.](#)

14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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
03/11/2014

PMR/PMC Development Template for Qudexy XR
PMR # 2137-1

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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

PMR/PMC Schedule Milestones: Final protocol Submission Date: _____
Study/Clinical trial Completion Date: _____
Final Report Submission Date: 03/2017
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

This formulation is required to support the PREA clinical studies.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

An age appropriate formulation is required to support the PREA clinical studies.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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

Required

- Observational pharmacoepidemiologic study
- Registry studies

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
Development of a new dosage form
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template for Qudexy XR
PMR # 2137-2

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>09/2017</u>
	Study/Clinical trial Completion Date:	<u>09/2020</u>
	Final Report Submission Date:	<u>04/2021</u>
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

This is a PREA study.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this study is to characterize the pharmacokinetics and tolerability of an age appropriate extended release formulation of topiramate in children ages 1 month to (b) (4). This information will inform dosing for the pivotal efficacy/safety trial in the specific age groups.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

**PMR/PMC Development Template for Qudexy XR
PMR # 2137-3**

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: An adequately controlled study to assess the efficacy and safety of the age appropriate formulation of Qudexy XR (topiramate) extended-release capsules, developed in PMR # 2137-1, as adjunctive therapy in children ages 1 month to less than 2 years old with partial onset seizures.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>07/2021</u>
	Trial Completion Date:	<u>07/2026</u>
	Final Report Submission Date:	<u>04/2027</u>
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

This is a PREA requirement.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal is to assess the efficacy and safety of the age appropriate formulation of Qudexy XR (topiramate) extended-release capsules, developed in PMR #2137-1, as adjunctive therapy in children ages 1 month to less than 2 years old with partial onset seizures.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 Pharmacokinetic studies or clinical trials
 Drug interaction or bioavailability studies or clinical trials
 Dosing trials
 Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 Immunogenicity as a marker of safety
 Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 Dose-response study or clinical trial performed for effectiveness
 Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 Are the objectives clear from the description of the PMR/PMC?
 Has the applicant adequately justified the choice of schedule milestone dates?
 Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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

/s/

SALLY U YASUDA
03/10/2014

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Final Label and Labeling Memo

Date: March 7, 2014

Reviewer: Jacqueline Sheppard, PharmD
Division of Medication Error Prevention and Analysis

Acting Team Leader: Julie Neshiewat, PharmD, BCPS
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Qudexy XR (Topiramate Extended-Release) Capsules
25 mg, 50 mg, 100 mg, 150 mg, 200 mg

Application Type/Number: NDA 205122

Applicant/sponsor: Upsher-Smith

OSE RCM #: 2014-102

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the revised container labels and carton labeling for Qudexy XR (Topiramate Extended-release) Capsules, NDA 205122, submitted on March 4, 2014 and March 6, 2014 (Appendices A to J). DMEPA previously reviewed the proposed labels and labeling under OSE Review # 2013-1237 dated October 21, 2013.

2 MATERIAL REVIEWED

DMEPA reviewed the labels and labeling received on March 4, 2014 and March 6, 2014. We compared the revised labels and labeling against the recommendations contained in OSE Review # 2013-1237 dated October 21, 2013 and emails dated February 21, 2014, February 25, 2014, and February 28, 2014.

3 CONCLUSIONS AND RECOMMENDATIONS

The revised labels and labeling adequately address our concerns from a medication error perspective. DMEPA concludes that the revised labels and labeling are acceptable.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Ermias Zerislassie at 301-796-0097.

14 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

JACQUELINE E SHEPPARD
03/07/2014

JULIE V NESHIEWAT
03/07/2014

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title¹	QUDEXY XR (topiramate) extended-release capsules for oral use
Applicant	UPSHER-SMITH LABORATORIES, INC.
Application/Supplement Number	NDA 205122
Type of Application	Original
Indication(s)	Partial Onset Seizures and Primary Generalized Tonic-Clonic Seizures and Lennox-Gastaut Syndrome
Office/Division	ODE I/DNP
Division Project Manager	Taura Holmes
Date FDA Received Application	February 11, 2013
Goal Date	March 11, 2014
Date PI Received by SEALD	March 5, 2014
SEALD Review Date	March 6, 2014
SEALD Labeling Reviewer	Elizabeth Donohoe
Acting SEALD Division Director	Sandra Kweder

¹ Product Title that appears in draft agreed-upon prescribing information (PI)

This Study Endpoints and Labeling Development (SEALD) Director sign-off review of the end-of-cycle, prescribing information (PI) for important format items reveals **outstanding format deficiencies** that should be corrected before taking an approval action. After these outstanding format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The Selected Requirements of Prescribing Information (SRPI) is a checklist of 42 important format PI items based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. The word “must” denotes that the item is a regulatory requirement, while the word “should” denotes that the item is based on guidance. Each SRPI item is assigned with one of the following three responses:

- **NO:** The PI does not meet the requirement for this item (**deficiency**).
- **YES:** The PI meets the requirement for this item (**not a deficiency**).
- **N/A:** This item does not apply to the specific PI under review (**not applicable**).

Selected Requirements of Prescribing Information

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- NO** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment: *The margin at the top of the page above Highlights is greater than 1/2 inch. The header must be removed in the final version; this should allow the Highlights heading to be moved up to meet the 1/2 inch margin requirement.*

- YES** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment: *There is a lot of white space between the horizontal line after the TOC and the beginning of FPI. To improve readability, consider moving FPI up to reduce the amount of white space.*

- NO** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment: *The headings for Adverse Reactions and Drug Interactions are not centered on the horizontal line.*

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Selected Requirements of Prescribing Information

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

Selected Requirements of Prescribing Information

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Selected Requirements of Prescribing Information

Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment: *The manufacturer's name is in all upper case; the Labeling Review Tool recommends avoiding use of all upper case. In this required statement, use of upper case for "SUSPECTED ADVERSE REACTIONS" serves to emphasize its importance and the use of upper case for the manufacturer's name detracts from the intended emphasis.*

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- NO** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment: *The revision date is missing and should state: "3/2014"*

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment: See SRPI item #32 regarding use of periods "." after section and subsection numbers in the FPI; the TOC uses the correct format.
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- NO** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: In the FPI, there are periods "." placed after each section number and subsection number (e.g., 1., 1.1.). These periods should be removed; the TOC has the correct format for section and subsection numbers.

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[see *Warnings and Precautions (5.2)*]” or “[see *Warnings and Precautions (5.2)*]”.

Selected Requirements of Prescribing Information

Comment: *There are cross-references to the Patient Counseling Information (PCI) section in subsections 5.2, 5.7, 8.9. A cross reference to the PCI section implies that there is additional information in that section. Section 17 should be based on information already stated in the FPI and therefore, is typically not cross referenced..*

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- YES** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Selected Requirements of Prescribing Information

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]

Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)]

[m/year]

[section (X.X)]

[m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

DOSAGE AND ADMINISTRATION

• [text]

• [text]

DOSAGE FORMS AND STRENGTHS

• [text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

1.1 [text]

1.2 [text]

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

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7 DRUG INTERACTIONS

7.1 [text]

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8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

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10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

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15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

ELIZABETH A DONOHOE
03/06/2014

ERIC R BRODSKY
03/06/2014

I agree. Eric Brodsky, SEALD labeling team leader, signing for Sandra Kweder, acting SEALD Division Director.

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: February 10, 2014

To: Eric Bastings, M.D.
Acting Director
Division of Neurology Products (DNP)

Taura Holmes, PharmD
Regulatory Project Manager
Division of Neurology Products (DNP)

From: Aline Moukhtara, RN, MPH, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Mathilda Fienkeng, PharmD, Team Leader
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 205122
OPDP PI and Carton and Container labeling comments for Topiramate
Extended-Release Capsules.

On November 8, 2013, DNP consulted OPDP to review the proposed package insert (PI), the Medication Guide, and carton and container labeling for the original NDA submission for Topiramate Extended-Release Capsules.

PI

Comments on the proposed PI are based on the version received via email from Taura Holmes (RPM) on January 16, 2014, entitled "NDA 205122 SCPI." Please note that OPDP's comments on the proposed PI are provided directly on the marked version below.

Medication Guide

A combined OPDP and DMPP patient labeling review was conducted and comments on the Medication Guide were sent under separate cover by DMPP on January 30, 2014.

Carton and Container Labeling

Since the proprietary name, (b) (4) has not been approved, we will not comment on the presentation of the proprietary name at this time.

If you have any questions, please contact Aline Moukhtara at 301-796-2841 or Aline.Moukhtara@fda.hhs.gov.

Thank you for the opportunity to comment.

Enclosure: Marked up PI and Carton and Container Labeling

93 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ALINE M MOUKHTARA
02/10/2014

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: January 30, 2014

To: Eric Bastings, MD
Acting Director
Division of Neurology Products (DNP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Shawna Hutchins, MPH, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Mathilda Fienkeng, PharmD
Team Leader
Office of Prescription Drug Promotion (OPDP)

From: Twanda Scales, RN, BSN, MSN/Ed.
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Aline M. Moukhtara, RN, MPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): BRANDNAME XR (topiramate)

Dosage Form and Route: Extended-Release Capsules, for Oral Use

Application Type/Number: NDA 205122

Applicant: Upsher-Smith Laboratories Inc.

1. INTRODUCTION

On February 11, 2013, Upsher-Smith Laboratories Inc., submitted for the Agency's review a New Drug Application (NDA 205122) for BRANDNAME XR (topiramate) extended-release capsules (25mg, 50mg, 100mg, 150mg, 200mg). The purpose of the submission was to seek approval for the added indications of:

- initial monotherapy in patients \geq 10 years of age with partial onset seizures (POS) or primary generalized tonic-clonic (PGTC) seizures
- adjunctive therapy for adults and pediatric patients (2 to 16 years of age) with partial onset seizures or primary generalized tonic-clonic seizures, and in patients \geq 2 years of age with seizures associated with Lennox Gastaut Syndrome (LGS)

On September 19, 2013, the Applicant submitted a labeling amendment to the pending New Drug Application (NDA 205122) for BRANDNAME XR (topiramate) extended-release capsules (25mg, 50mg, 100mg, 150mg, 200mg). The purpose of the submission was to provide updated draft labeling consistent with the changes requested in an email received from the Agency on September 03, 2013.

Topiramate was originally approved on December 24, 1996 for:

- the treatment of certain types of seizures (partial onset seizures and primary generalized tonic-clonic seizures) in people (b) (4)
- use with other medicines to treat certain types of seizures (partial onset seizures, primary generalized tonic-clonic seizures, and seizures associated with Lennox-Gastaut syndrome) in adults and children (b) (4)
- the prevention of migraine headaches in adults.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology Products (DNP) on November 07, 2013, and November 6, 2013 respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for BRANDNAME XR (topiramate) extended-release capsules.

2. MATERIAL REVIEWED

- Draft BRANDNAME XR (topiramate) extended-release capsules Medication Guide (MG) received on September 19, 2013 and received by DMPP on January 16, 2014.
- Draft BRANDNAME XR (topiramate) extended-release capsules MG received on September 19, 2013, and received by OPDP on January 16, 2014.
- Draft BRANDNAME XR (topiramate) extended-release capsules Prescribing Information (PI) received on September 19, 2013, revised by the Review Division throughout the current review cycle, and received by DMPP on January 16, 2014.

- Draft Prescribing Information (PI) received on September 19, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on January 16, 2014.
- Approved TOPAMAX (topiramate) comparator labeling dated October 29, 2012.
- Approved TROKENDI XR (topiramate) comparator labeling approved August 16, 2013.

3. REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4. CONCLUSIONS

The MG is acceptable with our recommended changes.

5. RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

TWANDA D SCALES
01/30/2014

ALINE M MOUKHTARA
01/30/2014

SHAWNA L HUTCHINS
01/30/2014

LASHAWN M GRIFFITHS
01/30/2014



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: January 17, 2014

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Taura Holmes, RPM
DNP

Subject: QT-IRT Consult to NDA 205122

This memo responds to your consult to us dated January 16, 2014 regarding the Sponsor's proposed labeling language. The QT-IRT received and reviewed the following materials:

- Your Consult
- Draft Labeling
- IRT Previous Review under IND 69257 (11/08/2011)
- Synopsis for Study 09-011

QT-IRT Comments for DNP

[REDACTED] (b) (4)

BACKGROUND

QT-IRT previously advised DNP that a thorough QT (TQT) study was not needed for the topiramate extended release (ER) formulation because no cardiac-related AEs were detected from post-marketing experience with the approved immediate release (IR) formulation and that the systemic exposure following ER formulation was lower compared to the IR formulation.

The Division is now in the process of reviewing labeling for NDA 205122 for the topiramate extended-release capsules. The Sponsor is proposing [REDACTED] (b) (4)

[REDACTED]

(b) (4)

[REDACTED]

[REDACTED]

Reviewer's Comments: [REDACTED] (b) (4)

[REDACTED]

Thank you for requesting our input into the development of this product under NDA 205122. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

KEVIN M KRUDYS
01/21/2014

NORMAN L STOCKBRIDGE
01/21/2014

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: November 6, 2013

TO: Eric P. Bastings, M.D.
Acting Director
Division of Neurology Products
Office of Drug Evaluation I

FROM: Xingfang Li, M.D., RAC
Consumer Safety Officer
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations
and
Michael F. Skelly, Ph.D.
Pharmacologist
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, R.Ph., Ph.D.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations
and
William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIRs Covering NDA 205-122, Topiramate
extended-release (ER) Capsules formulation (USL255)
200 mg, sponsored by Upsher-Smith Laboratories,
Inc.

At the request of the Division of Neurology Products,
Office of New Drugs, the Division of Bioequivalence and GLP
Compliance (DBGLPC) conducted inspections of the clinical
and analytical portions of the following study:

Study #: P09-003
Study Title: "A Randomized, Single-Center, Open-Label, 2-
way Crossover, Multi-Dose Pharmacokinetic
Study of USL255 in Healthy Adult Subjects"

Page 2 -NDA 205-122, Topiramate extended-release capsules, sponsored by Upsher-Smith Laboratories, Inc.

The audits included a thorough review of study records, examination of facilities and equipment, and interviews and discussions with the firms' management and staff.

Clinical Site:

The audit of the clinical portion was conducted at PPD Phase-I Clinic, Austin, TX (7/16-7/19/2013 by ORA Investigator Todd R. Lorenz). Following the inspection at the clinical site no Form FDA-483 was issued and there were no significant findings at the site.

Bioanalytical Site:

The audit of the analytical portion was conducted at (b) (4)

Following the inspections at the analytical site no Form FDA-483 was issued and there were no significant findings at the site.

Conclusions:

Following the above inspections, we recommend that data for clinical and analytical portions of study P09-003 are acceptable for further agency review.

Michael F. Skelly, Ph.D.
Pharmacologist

Xingfang Li, M.D., RAC
Consumer Safety Officer

Final Classifications:

Clinical

**NAI: PPD Phase-I Clinic, Austin, TX
FEI 3008374644**

Analytical

NAI: (b) (4)

Page 3 -NDA 205-122, Topiramate extended-release capsules,
sponsored by Upsher-Smith Laboratories, Inc.

CC:

CDER OSI PM TRACK

OSI/DBGLPC/Taylor/Bonapace/Choi/Mada/Dejernet

OSI/DBGLPC/Haidar/Skelly/Li

OMPT/CDER/OND/ODEI/DNP/Bastings/Holmes/Lana Chen

ORA/DAL-DO/HFR-SW150/Turcovski/Martinez/Mussawwir-Bias

ORA/DAL-DO/DAL-IB/AUS-TX/HFR-SW1575/Lorenz

ORA/BLT-DO/HFR-CE250/Richard-Math/Harris

ORA/BLT-DO/RIC-RP/HFR-CE2545/Milazzo

Draft: XFL 11/5/2013

Edit: MFS 11/6/2013

OSI: BE6460; O:\BE\EIRCOVER\205122.ups.top.doc

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/ Inspections/BE
Program/Clinical Sites/PPD, Austin, TX

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence &
Good Laboratory Practice Compliance/ Inspections/BE
Program/Analytical Sites/ (b) (4)

FACTS: (b) (4)

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/s/

XINGFANG LI
11/06/2013

SAM H HAIDAR
11/06/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: October 21, 2013

Reviewers: Sue (Liu) Liu, PharmD
Division of Medication Error Prevention and Analysis
Julie Neshiewat, PharmD
Division of Medication Error Prevention and Analysis

Team Leader Irene Z. Chan, PharmD, BCPS
Division of Medication Error Prevention and Analysis

Drug Name and Strengths: Topiramate Extended-release Capsules
25 mg, 50 mg, 100 mg, 150 mg, 200 mg

Application Type/Number: NDA 205122

Applicant: Upsher-Smith Laboratories

OSE RCM #: 2013-1237

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed labels and labeling for Topiramate extended-release capsules for areas of vulnerability that could lead to medication errors in response to a request from the Division of Neurology Products (DNP). This is a 505(b)(2) application, and the referenced drug is Topamax Tablets (NDA 020505).

1.1 PRODUCT INFORMATION

The Applicant provided the following product information in the September 19, 2013 submission.

- Active Ingredient: Topiramate
- Indication of Use:
 - Monotherapy Epilepsy: Initial monotherapy in patients ≥ 10 years of age with partial onset or primary generalized tonic clonic seizures
 - Adjunctive Therapy Epilepsy: Adjunctive therapy in patients ≥ 2 years of age with partial onset seizures or primary generalized tonic-clonic seizures, and seizures associated with Lennox-Gastaut syndrome (LGS)
- Route of Administration: Oral
- Dosage Form: Extended-release capsules
- Strength: 25 mg, 50 mg, 100 mg, 150 mg, 200 mg
- Dose and Frequency:

Indication	Initial Dose	Titration	Recommended Dose
Monotherapy			
In patients ≥ 10 years	50 mg once daily	Increase weekly by 50 mg for the first 4 weeks then 100 mg for weeks 5 to 6	400 mg once daily
Adjunctive Therapy			
In patients ≥ 17 with partial onset seizures or LGS	25 to 50 mg once daily	Increase dosage weekly by 25 to 50 mg	200 to 400 mg once daily
In patients ≥ 17 with primary generalized tonic-clonic seizures	25 to 50 mg once daily	Increase dosage weekly by 25 to 50 mg	400 mg once daily

In patients ≥ 2 with partial onset seizures, primary generalized tonic-clonic seizures or LGS	25 mg (or less, based on a range of 1 to 3 mg/kg /day) nightly for the first week	Increase dosage at 1- or 2-week intervals by 1 to 3 mg/kg once daily	5 to 9 mg/kg once daily
--	---	--	-------------------------

- How Supplied: Extended-release capsules contain beads of topiramate in a hard capsule and are available in the following package configurations

<i>Strength</i>	<i>Package Configurations</i>
25 mg	30, 90, 500 count
50 mg	30, 90, 500 count
100 mg	30, 90, 500 count
150 mg	30, 90, 500 count
200 mg	30, 90, 500 count

- Storage: Store in a tight container at 20°C to 25°C (68°F to 77°F). Excursions permitted between 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature]. Protect from moisture. Dispense in a tight container (b) (4)
- Container and Closure System: Not available

2 METHODS AND MATERIALS REVIEWED

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels and Carton Labeling submitted February 11, 2013 (Appendix A through Appendix J)
- Insert Labeling and Medication Guide submitted on September 19, 2013 (no image)

3 MEDICATION ERROR RISK ASSESSMENT

Our review of the labels and labeling determined there is inadequate strength differentiation within the product line. (b) (4)

Our review of the labels and labeling determined they can be improved for clarity and to increase the readability and prominence of important information on the label to promote the safe use of the product. We provide recommendations in Section 4.1 below.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

4 CONCLUSIONS

DMEPA concludes that there is inadequate strength differentiation within the product line. Additionally, the proposed label and labeling can be improved to promote the safe use of the product.

5 RECOMMENDATIONS

DMEPA provides the following comments for consideration by the review division prior to the approval of this NDA supplement:

5.1 COMMENTS TO THE DIVISION

A. Insert Labeling

1. The symbols $<$, \leq , $>$, \geq are utilized in the insert labeling to represent “less than,” “less than or equal to,” “greater than,” and “greater than or equal to” respectively. These symbols can be misinterpreted as the opposite of the intended symbol or mistakenly used as the incorrect symbol. We recommend that $<$ be replaced with “less than,” \leq be replaced with “less than or equal to,” $>$ be replaced with “greater than,” and \geq be replaced with “greater than or equal to”. For example, in the Highlights of Prescribing Information, revise (b) (4) to read “patients greater than or equal to 10 years of age” or “patients 10 years of age and older.”
2. When presenting numbers with symbols or units, insert a space between the number and the symbol, or unit, to provide better readability. Additionally, remove the symbol ‘/’ and insert the intended meaning. For example, in Section 2 Dosage and Administration, revise (b) (4) to read “400 mg per day.”
3. We recommend adding a unit of measure immediately following all numbers, as appropriate. For example, in Section 2 Dosage and Administration, revise (b) (4) to read “200 mg to 400 mg per day.”
4. In Section 2 Dosing and Administration, the adjunctive therapy dosing in patients 2 years of age and older with partial onset seizures, primary generalized tonic-clonic seizures or LGS states to initiate at 25 mg ((b) (4)) based on a range of 1 to 3 mg/kg per day). (b) (4)
(b) (4)

B. Medication Guide

1. To help distinguish this extended-release product from the marketed immediate-release topiramate products, we recommend adding a statement that this product is only administered once daily.
2. To emphasize that capsules should not be crushed or chewed, include a statement similar to “Capsules should not be crushed or chewed.”

3. For consistency with the insert labeling, we recommend revising the statement  (b) (4) to read “Store Brandname XR capsules at 59°F to 86°F (15°C to 30°C).”

5.2 COMMENTS TO THE APPLICANT

DMEPA advises the recommendations below be implemented prior to approval of this NDA.

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 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)
 We recommend you choose colors for the labels and labeling that are completely different from the capsule colors and are 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)

If you have further questions or need clarifications, please contact Ermias Zerislassie, project manager, at 301-796-0097.

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/s/

JULIE V NESHIEWAT
10/21/2013

IRENE Z CHAN
10/23/2013

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 07, 2013

TO: Director, Investigations Branch
Dallas District Office
4040 N. Central Expressway Suite 300
Dallas, TX 75204

Director, Investigations Branch
Baltimore District Office
6000 Metro Dr., Suite 101
Baltimore, MD 21215

FROM: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)

SUBJECT: FY 2013, **CDER High Priority User Fee NDA, Pre-Approval
Data Validation Inspection**, Bioresearch Monitoring,
Human Drugs, CP 7348.001

RE: NDA 205122
DRUG: Topiramate Extended-Release Capsules 25
mg, 50 mg, 100 mg, 150 mg, and 200 mg
SPONSOR: Upsher-Smith Laboratories, Inc., US
Maple Grove, MN

This memo requests that you arrange for inspections of clinical and analytical portions of the following bioequivalence study. Once an **ORA investigator is identified, please contact the DBGLPC point of contact (POC) listed at the end of this memo for background materials. A DBGLPC scientist with specialized knowledge may participate in the inspection of the analytical site to provide scientific and technical expertise. Please contact DBGLPC POC upon receipt of this assignment to arrange scheduling of the analytical inspection. Please complete the inspections prior to August 15, 2013.**

Do not notify the sites of the application number, the study to be inspected, drug name, or the study investigators prior to the start of the inspection. The information will be provided to the

Page 2 - BIMO Assignment, NDA 205122, Topiramate Extended-Release Capsules 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg

site(s) at the inspection opening meeting. **Please note that this inspection will be conducted under Bioresearch Monitoring Compliance Program CP 7348.001, not under CP 7348.811 (Clinical Investigators).**

At the completion of the inspection, please send a scanned copy of the completed sections A and B of this memo to Dr. Sam Haidar and the DBGLPC POC.

1. Study Number: P09-003
Study Title: "A randomized, single-center, open-label, 2-way crossover, multi-dose pharmacokinetic study of USL255 in healthy adult subjects"

Clinical Site: PPD Phase I Clinic
7551 Metro Center Drive
Building 10, Suite 200
Austin, TX 78744
TEL: (512)447-2985
FAX: (512)448-8879

Investigator: Ikenna Ogbaa, M.D.

Contact Person: Tiffany Reyes
Sr. Project Manager

SECTION A

RESERVE SAMPLES: Because this is bioequivalence study subject to 21 CFR 320.38 and 320.63, the site conducting the study is responsible for randomly selecting and retaining reserve samples from the shipments of drug product provided by the sponsor for subject dosing.

Please note that the final rule for "Retention of Bioavailability and Bioequivalence Testing Samples" (Federal Register, Vol. 58, No. 80, pp. 25918-25928, April 28, 1993) specifically addresses the requirements for bioequivalence studies

(<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm120265.htm>).

Please refer to CDER's "Guidance for Industry, Handling and Retention of BA and BE Testing Samples" (May 2004), which clarifies the requirements for reserve samples

(<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf>).

Please follow the instructions below:

- Verify if reserve samples were retained according to regulations.
- If the reserve samples were stored at a third party site, please verify and collect an affidavit to confirm that the third party is independent from the sponsor, manufacturer, and packager, and that the sponsor was notified in writing of the location. In an event the reserve samples were not retained or are not adequate in quantity, please notify the POC immediately.
- Please obtain a written assurance from the clinical investigator or the responsible person at the clinical site that the reserve samples are representative of those used in the specific bioequivalence study, and that they were stored under conditions specified in accompanying records. Document the signed and dated assurance [21 CFR 320.38(d, e, g)] on the facility's letterhead, or Form FDA 463a, Affidavit.
- Samples of the test and reference products in their original containers should be collected and shipped to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening, at the following address:

Benjamin Westenberger, Ph.D.
Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis (DPA)
Center for Drug Analysis (HFH-300)
US Courthouse and Customhouse Bldg.
1114 Market Street, Room 1002
St. Louis, MO 63101
TEL: (314) 539-2135

SECTION B

Please confirm the informed consent and records for 100% of subjects enrolled at the site. The study records in the NDA submission should be compared to the original documents at the site. Include a description of your findings in the EIR.

Data Audit Checklist:

- Evidence of under-reporting of AEs identified? _____
- Evidence of inaccuracy in electronic data capture? _____
- Presence of 100% of signed and dated informed consent forms: _____
- Reports for the subjects audited: _____

- Number of subject records reviewed during the inspection:_____
 - Number of subjects screened at the site:_____
 - Number of subjects enrolled at the site:_____
 - Number of subjects completing the study:_____
 - Verify from source documents that evaluations related to the primary endpoint were accurately reported in case report forms:_____
 - Confirm that clinical assessments were conducted in a consistent manner and in accordance with the protocol:_____
 - Confirm that SOPs were followed during study conduct:_____
 - Examine correspondence files for any sponsor- or monitor-requested changes to study data or reports:_____
 - Include a brief statement summarizing your findings (IRB approvals, study protocol and SOPs, protocol deviations, adverse events, concomitant medications, inclusion/exclusion criteria, adequacy of records, drug accountability documents, and case report forms for dosing of subjects, etc.)
 - Other Comments:
-
-

Collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

Analytical Site:

(b) (4)

Investigator:

(b) (4)

Methodology:

LC-MS/MS

Please confirm the following during the inspection:

- Examine all pertinent items related to the analytical methods used for the measurement of **topiramate concentrations in human plasma**.
- Compare the accuracy of the analytical data provided in the NDA submission by the applicant with the original documents at the site.

- Determine if the validated analytical method was employed for the subject sample analysis.
- Compare the assay parameters (such as variability between and within runs, accuracy and precision, etc.) observed during the study sample analysis with those obtained during method validation.
- Confirm that the accuracy and precision in matrix were determined using standards and (b) (4) prepared from separate stocks.
- Determine if the subject samples were analyzed within the validated stability period.
- Confirm that freshly made (b) (4) and/or freshly made (b) (4) were used for stability evaluations during method validation.
- Confirm that the precision and accuracy was demonstrated at least one time using (b) (4) and (b) (4) prepared from separate stock solutions.
- Scrutinize the number of repeat assays of the subject plasma samples, the reason for such repetitions, the SOP(s) for repeat assays, and if relevant stability criteria such as the number of freeze-thaw cycles sufficiently covered the stability of reanalyzed subject samples.
- Examine correspondence files between the analytical site and the sponsor for their content.

Additional instructions to ORA Investigator:

In addition to the compliance program elements, other study specific instructions may be provided by the DBGLPC POC prior to the inspection. Therefore, we request that the DBGLPC POC be contacted for further instructions, inspection-related questions or clarifications before the inspection, and also regarding data anomalies or questions noted during review of study records on site.

Please fax/email a copy of Form FDA 483 if issued, as soon as possible. If at close-out of the inspection, it appears that the violations may warrant an OAI classification, please notify the DBGLPC POC as soon as possible. At completion of inspection, please remind the inspected entity of the 15 business-day timeframe for submission of a written response to observations listed on Form FDA 483. Please forward any written response as soon as you receive it to Dr. Sam H. Haidar (Fax: 1-301-847-8748 or Email: sam.haidar@fda.hhs.gov) and the DBGLPC POC. Please address the EIR to Dr. Haidar:

Page 6 - BIMO Assignment, NDA 205122, Topiramate Extended-Release Capsules 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg

Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)
Office of Compliance
Bldg. 51 Rm. 5330
10903 New Hampshire Ave.
Silver Spring, MD 20993

DBGLPC POC: Ruben Ayala, Pharm.D.
Email: ruben.ayala@fda.hhs.gov
TEL: (301)796-2018
FAX: (301)847-8748

CC:

CDER OSI PM TRACK

OSI/DBGLPC/Taylor/Haidar/Ayala/Patel/Choi/Dejernett

CDER/OND/ODEI/DNP/Holmes/Chen/Dinsmore

HFR-SW150/Turcovski, Susan (DIB)

HFR-SW1540/Martinez, Joel (BIMO)

HFR-SW1515/Alanna Mussawwir-Bias

HFR-CE250/Richard-Math, Connie (DIB)/Harris, Cynthia (BIMO)

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Laboratory Practice Compliance/Electronic Archive/BEB

FACTS: (b) (4)

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

/s/

RUBEN C AYALA
05/07/2013

MICHAEL F SKELLY
05/07/2013
Skelly signing on behalf of Dr. Haidar