UPSHER-SMITH

May 28, 2024

RESPONSE TO PREA NON-COMPLIANCE LETTER

REQUEST FOR WAIVER OF PEDIATRIC STUDIES

Paul R. Lee, MD, PhD, Director
Division of Neurology 2
Office of Neuroscience
Center for Drug Evaluation and research
U.S. Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 205122 – Sequence 0207
QUDEXY® XR (topiramate) Extended-Release Capsules
Response to PREA Non-Compliance Letter /Request for Waiver of Pediatric Studies

Dear Dr. Lee

Reference is made to NDA 205122 QUDEXY® XR (topiramate) Extended-Release Capsules, approved on March 11, 2014. Further reference is made to the FDA's letter – Notification of Non-Compliance with PREA dated April 22, 2024, for the below postmarketing requirement (PMR):

2137-4: A study to evaluate the pharmacokinetics (PK) and tolerability of the age-appropriate formulation of Qudexy XR (topiramate) extended-release capsules as adjunctive therapy in children ages 6 months to less than 2 years with partial-onset seizures (POS).

Upsher-Smith Laboratories, LLC (Upsher-Smith) hereby submits a formal response to the above reference PREA non-compliance letter and request a waiver of pediatric studies (PMR 2137-4) based on justification provided below.

As per PMR timeline commitment, Upsher-Smith submitted a draft protocol to evaluate children, ages between 6 months to 2 years old for PMR 2137-4 (IND 069257, Sequence 0080) on March 29, 2019. FDA responded with comments via email on August 16, 2019. Upsher-Smith subsequently responded on August 29, 2019 (Sequence 0082) stating that we did not agree with the Agency's request to (b) (4) No further comments were received from FDA since then.

Upsher-Smith initiated the study activities by reaching out to Investigators in the United States and CROs. The Investigators showed little to no interest in conducting this study. There were several reasons for a lack of interest in conducting this pharmacokinetic study. The primary reason being the safety of Topiramate in infants with Partial Onset Seizures (POS). At that time, the Warnings and Precautions section of all topiramate products summarized specific adverse events

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for the population less than 2 years of age including increased incidence of hyperammonemia, reductions from baseline in length, weight, and head circumference, and kidney stones. In addition, (b) (4)

Upsher-Smith shared with FDA the potential Investigator's safety concerns of conducting a clinical study in infants less than 2 years of age. (b) (4)

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The Warnings and Precautions section of the Reference Listed Drug, Topamax, were modified in 2022 with significant additional safety information for pediatric patients. The Warnings and Precautions section of Qudexy XR was subsequently updated and approved in December 2022 (Supplement 014). The additional safety concerns for children were based on a one-year, active-controlled study of pediatric patients with immediate-release topiramate. The changes included revisions to two existing sections in Warnings and Precautions and two entirely new sections in the Warnings and Precautions section along with additional changes in other sections. The changes are identified below.

Warnings and Precautions added to the Qudexy XR labeling, approved December 2022 (NDA205122/S-014)

Section 5.4 Metabolic Acidosis [New text added]

…… A one-year, active-controlled study of pediatric patients treated with immediate-release topiramate demonstrated that topiramate decreased lumbar spine bone mineral density and that this lumbar spine bone mineral density decrease was correlated (using change from baseline for lumbar spine Z score at final visit versus lowest post-treatment serum bicarbonate) with decreased serum bicarbonate, a reflection of metabolic acidosis [*see Warnings and Precautions (5.9, 5.13)*].

Section 5.9 Decrease in Bone Mineral Density [New section added]

Results of a one-year active-controlled study in pediatric patients (N=63) demonstrated negative effects of immediate-release topiramate monotherapy on bone mineral acquisition via statistically significant decreases in bone mineral density (BMD) measured in lumbar spine and in total body less head *[see Use in Specific Populations (8.4)]*. Twenty-one percent of topiramate-treated patients experienced clinically important reductions in BMD (Z score change from baseline of –0.5 or greater) compared to 0 patients in the control group. Although decreases in BMD occurred across all pediatric age subgroups, patients 6 to 9 years of age were most commonly affected. The sample size and study duration were too small to determine if fracture risk is increased. Decreased BMD in the lumbar spine was correlated with decreased serum bicarbonate, which commonly occurs with topiramate treatment and reflects metabolic acidosis, a known cause of increased bone resorption *[see Warnings and Precautions (5.4)]*. Although small decreases in some markers of bone metabolism (e.g., serum alkaline phosphatase, calcium, phosphorus, and 1,25-dihydroxyvitamin D) occurred in topiramate-treated patients, more significant decreases in serum parathyroid hormone and 25-hydroxyvitamin D, hormones involved in bone metabolism, were observed, along with an increased excretion of urinary calcium.

Section 5.10 Negative Effects on Growth (Height and Weight) [New section]
Results of a one-year active-controlled study of pediatric patients (N=63) demonstrated negative effects of immediate-release topiramate monotherapy on growth (i.e., height and weight) *[see Use in Specific Populations (8.4)]*. Although continued growth was observed in both treatment groups, the topiramate group showed statistically significant reductions in mean annual change from baseline in body weight compared to the control group. A similar trend of attenuation in height velocity and height change from baseline was also observed in the topiramate group compared to the control group. Negative effects on weight and height were seen across all topiramate age subgroups. Growth (height and weight) of children receiving prolonged topiramate therapy should be carefully monitored.

Section 5.13 Kidney Stones [New paragraph added]
An increase in urinary calcium and a marked decrease in urinary citrate was observed in immediate-release topiramaate-treated pediatric patients in a one-year active-controlled study [See Use in Specific Populations (8.4)]. This increased ratio of urinary calcium/citrate increases the risk of kidney stones and/or nephrocalcinosis.

Additional changes added to the Qudexy XR labeling, approved December 2022 (NDA205122/S-014)
Section 8.4 Pediatric Use [New text added]
Monotherapy Treatment in Patients 2 Years of Age and Older
The safety and effectiveness for partial-onset seizures have been established in pediatric patients aged 2 years and older *[see Adverse Reactions (6.1), Clinical Studies (14.1)]*.

A one-year, active-controlled, open-label study with blinded assessments of bone mineral density (BMD) and growth in pediatric patients 4 to 15 years of age, including 63 patients with recent or new onset of epilepsy, was conducted to assess effects of immediate-release topiramate (N=28, 6-15 years of age) versus levetiracetam (N=35, 4-15 years of age) monotherapy on bone mineralization and on height and weight, which reflect growth. Effects on bone mineralization were evaluated via dual-energy X-ray absorptiometry and blood markers. Table 10 summarizes effects of topiramate at 12 months for key safety outcomes including BMD, height, height velocity, and weight. All Least Square Mean values for topiramate and the comparator were positive. Therefore, the Least Square Mean treatment differences shown reflect a topiramate-induced attenuation of the key safety outcomes. Statistically significant effects were observed for decreases in BMD (and bone mineral content) in lumbar spine and total body less head and in weight. Subgroup analyses according to age demonstrated similar negative effects for all key safety outcomes (i.e., BMD, height, weight).

Table 11: Summary of Immediate-release Topiramate Treatment Difference Results at 12 Months for Key Safety Outcomes

Safety Parameter	Treatment Difference in Least Square Means (95 % Confidence Interval)
Annual Change in BMD Lumbar Spine (g/cm^2)	-0.036 (-0.058, -0.014)

Annual Change in BMD TBLH* (g/cm^2)	-0.026 (-0.039, -0.012)
Annual Change in Height (cm) (4 to 9 years, Primary Analysis Population for Height)**	-0.84 (-2.67, 0.99)
Annual Change in Height (cm) (4 to 15 years)	-0.75 (-2.21, 0.71)
Annual Change in Height (cm) (10 to 15 years)	-1.01 (-3.64, 1.61)
Height Velocity (cm/year) (4 to 9 years)	1.00 (-2.76, 0.76)
Height Velocity (cm/year) (4 to 15 years)	-0.98 (-2.33, 0.37)
Height Velocity (cm/year) (10 to 15 years)	-0.96 (-3.24, 1.32)
Annual Change in Weight (kg)	-2.05 (-3.66, -0.45)

* TBLH = total body less head

** Whereas no patients were randomized to 2 to 5 year of age subgroup for topiramate, 5 patients (4 to 5 years) were randomized to the active control group.

Metabolic acidosis (serum bicarbonate < 20 mEq/L) was observed in all topiramate-treated patients at some time in the study [see Warnings and Precautions (5.4)]. Over the whole study, 76% more topiramate-treated patients experienced persistent metabolic acidosis (i.e. 2 consecutive visits with or final serum bicarbonate < 20 mEq/L) compared to levetiracetam treated patients. Over the whole study, 35% more topiramate-treated patients experienced a markedly abnormally low serum bicarbonate (i.e., absolute value < 17 mEq/L and ≥ 5 mEq/L decrease from pre-treatment), indicating the frequency of more severe metabolic acidosis, compared to levetiracetam -treated patients. The decrease in BMD at 12 months was correlated with decreased serum bicarbonate, suggesting that metabolic acidosis was at least a partial factor contributing to this adverse effect on BMD.

Topiramate-treated patients exhibited an increased risk for developing an increased serum creatinine and an increased serum glucose above the normal reference range compared to control patients.

Section 17 Patient Counseling Information [New paragraphs added]
Decrease in Bone Mineral Density

Inform the patient or caregiver that long-term treatment with QUDEXY XR can decrease bone formation and increase bone resorption in children *[see Warnings and Precautions (5.9)]*.

Negative Effects on Growth (Height and Weight)

Discuss with the patient or caregiver that long-term QUDEXY XR treatment may attenuate growth as reflected by slower height increase and weight gain in pediatric patients *[see Warnings and Precautions (5.10)]*.

Request for Waiver of Pediatric Studies

Due to the expanded safety concerns that need to be identified in the Informed Consent, Upsher-Smith has not been able to identify Investigators interested in conducting a clinical study with pharmacokinetic endpoints with Qudexy XR in infants 6 to 24 months of age in the United States. This product is not approved or marketed outside of the United States (b) (4) As presented above, significant safety issues have been observed in this age population,

including metabolic acidosis, hyperammonemia or abnormal ammonia values, growth-related adverse events, behavioral impairments, and changes in clinical laboratory findings.

Based upon the reasons presented above, pursuant to the FD&C Act, section 505B (a)(4)(B), Upsher-Smith Laboratories, LLC (Upsher-Smith) requests waiver of conducting pediatric study (PMR 2137-4) referenced above. The necessary studies are impossible or highly impracticable due to the identified safety concerns.

We request that information related to this application be treated as confidential within the meaning of 21 CFR 314.430, and that no information, except as provided in 21 CFR 314.430, be released without our written consent.

All files have been checked for viruses using Carbon Black Cloud Protection and no viruses detected. The submission is approximately 5 MBs. If there are any technical issues, please contact Stephen Thais at stephen.thais@upsher-smith.com or (484) 574- 4432.

If you have any questions concerning this submission, please contact me via phone or email.

Sincerely,

Ronak Patel
Associate Director, Regulatory Affairs, CMC
Upsher-Smith Laboratories, LLC
6701 Evenstad Drive
Maple Grove, MN 55369
Fax: (763) 315-2578
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NDA 205122

NOTIFICATION OF
NON-COMPLIANCE WITH PREA

Upsher-Smith Laboratories, LLC
Attention: Ronak Patel
Associate Director, Regulatory Affairs, CMC
6701 Evenstad Drive N
Maple Grove, MN 55369

Dear Ronak Patel:

Please refer to your new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the Act) for Qudexy XR (topiramate extended-release) capsules, which was approved on March 11, 2014.

The Agency has determined that you have failed to meet the postmarketing requirement (PMR) of the Pediatric Research Equity Act (PREA) for this application because you have not yet submitted your pediatric assessment for PMR 2137-4, which was deferred until October 31, 2022. Therefore, we are hereby notifying you that due to your failure to submit either a pediatric assessment or a request for a deferral extension, you are not in compliance with federal law.

Under the provisions of section 505B(d)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) [21 U.S.C. 355c(d)(1)], you must respond in writing within 45 calendar days of the date of this letter. Your response should include the reason(s) for the delayed pediatric assessment and a date by which you expect to submit the assessment. You may also include a request for a deferral extension, if applicable, which should be identified as a "**DEFERRAL EXTENSION REQUESTED**" in your response.

In accordance with the FD&C Act, FDA will post this letter and your response to the website at https://www.fda.gov/drugs/development-resources/non-compliance-letters-under-505bd1-federal-food-drug-and-cosmetic-act with redactions for any trade secrets and confidential commercial information 60 calendar days from the date of this letter.

Please identify your response to this letter as a "**RESPONSE TO PREA NON-COMPLIANCE LETTER.**" To facilitate our review, submit this information to your NDA with a cross-reference letter to the investigational new drug application (IND) to which your protocol has been submitted.

If you have any questions, please contact Alina Walizada, Regulatory Project Manager, at alina.walizada@fda.hhs.gov .

Sincerely,

{See appended electronic signature page}

Paul R. Lee, MD, PhD
Director
Division of Neurology 2
Office of Neuroscience
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PAUL R LEE
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