



NDA 20-505, 20-844

INDs 28,549; 49,640; [REDACTED] 60,913; [REDACTED]

The R.W. Johnson
Pharmaceutical Research Institute
Attention: Ms. Catherine Glamkowski
Route 202, P.O. Box 300
Raritan, NJ 08869-0602

Dear Ms. Glamkowski:

Reference is made to your Proposed Pediatric Study Request (PPSR) submitted on August 3, 2001 for topiramate to NDAs 20-505 and 20-844 and INDs 28,549; 49,640; [REDACTED]; 60,913; [REDACTED], and to your PPSR amendment submitted November 7, 2001.

To obtain needed pediatric information on topiramate, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following studies (described below) to support adjunctive use in the treatment of epilepsy (ages 1 month to 2 years for partial seizures and ages 6 months to 2 years for primary generalized tonic-clonic seizures).

For each indication we are asking for information from three types of studies:

Study Type I: Pediatric~ Pharmacokinetic/Tolerability Study

Study Type II: Pediatric Efficacy and Safety Study

Study Type III: Pediatric One Year Safety Study

TYPE I STUDIES: PHARMACOKINETIC AND TOLERABILITY STUDIES

You must obtain pharmacokinetic data to provide information pertinent to dosing of the study drug in the relevant pediatric population. In addition, you should perform preliminary multiple dose tolerability studies (in which kinetic data can be obtained) to fully explore the range of tolerated doses, before conducting the definitive efficacy and safety studies. Adequate pharmacokinetic and tolerability data from studies in a single indication would be sufficient to meet this requirement.

Patient Age Groups:

- Children with Partial Seizures – 1 month (full term) to 2 years of age, inclusive
- Children with Primary Generalized Tonic-Clonic Seizures – 6 months (full term) to 2 years of age, inclusive

Study Design:

Multiple dose tolerability stud(ies) should explore the range of tolerated doses. PK data can be obtained from these studies using sparse sampling approaches. This may also include the use of data from different studies (including the efficacy studies). If a sparse sampling approach is used, approximately 3-4 blood samples per patient should be collected, with each sample collected during a separate phase of the full concentration-time profile. Blood samples in population PK studies should not be collected at fixed time points.

You should be aware that a draft guidance document on pediatric pharmacokinetic studies is available at [www.fda.gov/cder/guidance/1970dft.pdf] and a guidance document on population pharmacokinetic studies is available under [www.fda.gov/cder/guidance/1852fnl.pdf].

Number of Patients to be Studied or Power of the Study to be Achieved

Sufficient numbers of subjects must be studied to adequately characterize the pharmacokinetics of topiramate within the specified age ranges and to detect pharmacokinetic drug interactions, effects of covariates (see study endpoints below), and dose effects. A larger number would be needed to perform sparse sampling than for traditional PK studies. A relatively uniform distribution of patients throughout the age range should be studied.

Drug Information:

Dosage form(s): Age appropriate topiramate immediate release formulations e.g., sprinkle capsules and possibly a liquid formulation for younger children (n.b. the formulations used should be the same as used in the efficacy and safety trials). If different immediate release formulations are used in the clinical trials, comparable bioavailability and absorption characteristics between the formulations should be established.

Route of administration: Oral

Study Endpoints:

Topiramate pharmacokinetic metrics, such as C_{max}, t_{max}, AUC, t_{1/2}, apparent clearance (CL/F), and apparent volume of distribution (V/F) and other metrics as appropriate should be calculated. Potential effects of covariates such as dose, age, body-weight, body-surface area, and renal function should be included in the analysis, and used in the dosing recommendations if deemed appropriate. The potential influence of other covariates such as race, gender, formulation, or concomitant medications, on pharmacokinetic metrics should also be investigated. These covariates may be studied using population pharmacokinetics as part of the efficacy and safety studies.

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Statistical Information:

Statistical information should include descriptive statistics of topiramate pharmacokinetic parameters. These results should be compared to pharmacokinetic metrics obtained in adults (the use of adult historical control data is acceptable).

TYPE II STUDIES: EFFICACY AND SAFETY STUDIES

Safety and Efficacy Studies are required for each of the two indications. These are summarized below.

Partial Seizures

Type of Study

Pediatric Efficacy and Safety Study

Objectives/Rationale

To establish the efficacy and short-term safety of Topamax as adjunctive therapy in the treatment of partial seizures in pediatric patients ages 1 month to 2 years.

Indication to be Studied

The use of Topamax for the adjunctive treatment of partial seizures in pediatric patients, ages 1 month to 2 years

Study Design

Randomized, double-blind, placebo-controlled, parallel group, efficacy and short-term safety outpatient study. The trial must maximize the opportunity to detect a treatment effect of the drug, if there is one in this population. Specifically, if you perform a flexible dose ranging study or a fixed dose study that does not fully explore the range of tolerable doses in this population and that study fails to detect an effect of the drug, this will not be considered to have met the requirements of this request. Therefore, we strongly recommend that the trial be a fixed dose study that includes fixed doses that fully explore the tolerated dose range in this population.

Age Groups to be Studied

Pediatric patients ages 1 month (full term) to 2 years.

Dose Selection

An age-appropriate dosing regimen for this study must be based on relevant data from the pharmacokinetic studies described in this Written Request.

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Number of Patients to be Studied or Power of the Study to be Achieved

A sufficient number of pediatric patients with partial seizures to be able to detect a clinically and statistically significant difference between treatment and control on a valid measure of seizure prevention. The study must be powered using the effect size observed in the pivotal studies in adults and children age 2 years to 16 years. The study must have at least 80% power to detect a treatment effect of that size.

Entry Criteria (i.e., inclusion/exclusion criteria)

Pediatric patients ages 1 month to 2 years with refractory partial seizures, uncontrolled on one or more standard AEDs. Enrollment will generally reflect the gender, age, and racial distribution concordant with this patient population.

Clinical Endpoints

A single standard measure of seizure frequency and measures of clinical safety as defined in SAFETY section.

Drug Information

An age appropriate formulation must be used in the studies described above. Any unapproved formulation will need to be supported by a study of relative bioavailability; these studies may be conducted in adults. A formulation you develop for use in children should meet standards for marketing approval. If you cannot develop a potentially marketable formulation, you will need to document the attempt to do so, and the Agency will consider another formulation that is standardized and palatable. Full study reports of any relative bioavailability studies should be submitted to the Agency.

Dosage form: Age-appropriate formulation for younger patients.

Route of administration: Oral

Regimen: To be determined by the development plan

Statistical Information, Including Statistical Assessments

Assessment of the between group difference on a standard measure of partial seizure frequency by a statistical methodology appropriate to the data generated and a descriptive analysis of the safety data.

Labeling That May Result from this Study

The pediatric epilepsy efficacy and safety study described in this request may result in the addition to labeling of information pertinent to this study.

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Primary Generalized Tonic-Clonic Seizures

Type of Study

Pediatric Efficacy and Safety Study

Objectives/Rationale

To establish the efficacy and short-term safety of Topamax as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in pediatric patients ages 6 months to 2 years.

Indication to be Studied

The use of Topamax for the adjunctive treatment of primary generalized tonic-clonic seizures in pediatric patients, ages 6 months to 2 years

Study Design

Randomized, double-blind, placebo-controlled, parallel group, efficacy and short-term safety outpatient study. The trial must maximize the opportunity to detect a treatment effect of the drug, if there is one in this population. Specifically, if you perform a flexible dose ranging study or a fixed dose study that does not fully explore the range of tolerable doses in this population and that study fails to detect an effect of the drug, this will not be considered to have met the requirements of this request. Therefore, we strongly recommend that the trial be a fixed dose study that includes fixed doses that fully explore the tolerated dose range in this population.

Age Groups to be Studied

Pediatric patients ages 6 months (full term) to 2 years.

Dose Selection

An age-appropriate dosing regimen for this study must be based on relevant data from the pharmacokinetic studies described in this Written Request.

Number of Patients to be Studied or Power of the Study to be Achieved

A sufficient number of pediatric patients with primary generalized tonic-clonic seizures to be able to detect a clinically and statistically significant difference between treatment and control on a valid measure of seizure prevention. The study must be powered using the effect size observed in the pivotal studies in adults and children age 2 years to 6 years. The study must have at least 80% power to detect a treatment effect of that size.

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Entry Criteria (i.e., inclusion/exclusion criteria)

Pediatric patients ages 6 months to 2 years with refractory primary generalized tonic-clonic seizures, uncontrolled on one or more standard AEDs. Enrollment must generally reflect the gender, age, and racial distribution concordant with this patient population.

Clinical Endpoints

A single standard measure of seizure frequency and measures of clinical safety as defined in SAFETY section.

Drug Information

An age appropriate formulation must be used in the studies described above. Any unapproved formulation will need to be supported by a study of relative bioavailability; these studies may be conducted in adults. A formulation you develop for use in children should meet standards for marketing approval. If you cannot develop a potentially marketable formulation, you will need to document the attempt to do so, and the Agency will consider another formulation that is standardized and palatable. Full study reports of any relative bioavailability studies should be submitted to the Agency.

Dosage form: Age-appropriate formulation for younger patients.

Route of administration: Oral

Regimen: To be determined by the development plan

Statistical Information, Including Statistical Assessments

Assessment of the between group difference on a standard measure of primary generalized seizure frequency by a statistical methodology appropriate to the data generated and a descriptive analysis of the safety data.

Labeling That May Result from this Study

The pediatric epilepsy efficacy and safety study described in this request may result in the addition to labeling of information pertinent to this study.

TYPE III STUDIES: SAFETY

Safety data must be collected in all of the controlled efficacy trials for the above indications. Routine safety assessments must be collected at baseline and appropriate follow-up times. i.e. vital signs, weight, height (using a stadiometer), clinical laboratory measures, ECGs, and monitoring for adverse events.

Safety concerns deserving special attention include: oligohydrosis, hyperthermia, acidosis, kidney stones (requiring periodic ultrasound during treatment). hepatotoxicity and hyperammonemia (baseline

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LFTs and ammonia levels with monthly follow-up testing for 3 months), rash, cognitive/neuropsychiatric adverse events, and effects on growth.

For the partial seizure indication (and this will also fulfill the requirement for the primary generalized seizure indication), a minimum of 100 patients, age 1 month to 2 years must be exposed to study drug for one year. The long-term safety data must be at or above the dose or doses identified as effective in an adequately designed trial, as described above. If an adequately designed and conducted effectiveness trial fails to detect a drug effect, you must still collect long-term safety data, at doses at least as high as the doses currently used in treating patients off-label with this drug.

FORMAT OF REPORTS TO BE SUBMITTED

Full study reports or analyses, not previously submitted to the Agency, addressing the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies must be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity one of the following designations must be used: Hispanic/Latino or Not Hispanic/Latino.

TIMEFRAME FOR SUBMITTING REPORTS OF THE STUDIES

Reports of the above studies must be submitted to the Agency on or before June 30, 2007, to be eligible to qualify for pediatric exclusivity extension under Section 505A of the Act. Please remember that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of studies in response to this Written Request.

RESPONSE TO WRITTEN REQUEST:

As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies must be submitted **as a new drug application or as a supplement to an approved NDA** with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your

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submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, Dissemination of Pediatric Information, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. the type of response to the Written Request (complete or partial);
2. the status of the supplement (withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, approvable, not approvable); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at <http://www.fda.gov/cder/pediatric/Summaryreview.htm> and publish in the Federal Register a notification of availability

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request must be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, call Lana Chen, Regulatory Project Manager, at 301-594-5529.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I

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

/s/

Robert Temple
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