DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-505; NDA 20-844
IND 28,549; IND 49,640
IND [redacted]; IND 60,913; IND [redacted]

WRITTEN REQUEST – AMENDMENT 2

Ortho-McNeil Pharmaceutical, Inc.
c/o Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Attention: Catherine M. Glamkowski
Associate Director, Regulatory Affairs
920 Route 2020 South; P.O. Box 300
Raritan, New Jersey 08869-0602

Dear Ms. Glamkowski:

Please refer to your correspondence dated January 13, 2005 and February 2, 2005, requesting changes to FDA's July 9, 2004, Written Request for pediatric studies for topiramate.

We have reviewed your proposed changes and are amending the Written Request. For convenience, the full text of the Written Request, as amended, follows. This Written Request supercedes the Written Request dated July 9, 2004.

To obtain needed pediatric information on topiramate, the 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 24 months, inclusive) for partial seizures.

For this 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

STUDY TYPE I: PHARMACOKINETIC AND TOLERABILITY STUDY

You must obtain pharmacokinetic data to provide information pertinent to dosing of the study drug in the relevant pediatric population. In particular, you must collect pharmacokinetic and tolerability data as outlined below, in a separate pharmacokinetic study and in a controlled efficacy study with an open-label extension component collecting long-term safety data.

Patient Age Groups:

- Children with Partial Seizures – 1 month (corrected age of at least 44 weeks gestational age) to 24 months, inclusive

Study Design:

Pharmacokinetic data can be obtained 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 must 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 pharmacokinetic studies. A relatively uniform distribution of patients throughout the age range must 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 must be established.

Route of administration: Oral

Regimen: To be determined by the development plan

- If the studies you conduct in response to this Written Request demonstrate this drug will benefit children, then an age-appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and testing a new dosage form for which you will seek approval for commercial marketing. If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients.

Development of a commercially marketable formulation is preferable. Any new commercially marketable formulation you develop for use in children must meet agency standards for marketing approval.

If you cannot develop a commercially marketable age-appropriate formulation, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product label upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies should be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

Study Endpoints:

Topiramate pharmacokinetic metrics, such as Cmax, tmax, AUC, t1/2, apparent clearance (CL/F), and apparent volume of distribution (V/F) and other metrics as appropriate must be calculated. Potential effects of covariates such as dose, age, body-weight, body-surface area, and renal function must 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 must also be investigated. These covariates may be studied using population pharmacokinetics as part of the efficacy and safety studies.

Statistical Information:

Statistical information must 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).

STUDY TYPE II: EFFICACY AND SAFETY STUDY

A Safety and Efficacy Study is required for this indication. This study is 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 (corrected age of at least 44 weeks gestational age) to 24 months, inclusive

Indication to be Studied:

The use of Topamax for the adjunctive treatment of partial seizures in pediatric patients, ages 1 month (corrected age of at least 44 weeks gestational age) to 24 months, inclusive

Study Design:

Randomized, double-blind (and rater-blinded), placebo-controlled, parallel group, efficacy and short-term safety outpatient study. We strongly recommend that the trial be a fixed dose study that includes fixed doses (5, 15, and 25 mg/kg/day) as suggested by the literature, previous experience of the Sponsor, clinical practice experience with topiramate in infants, consultation with the Agency, and practical constraints to maximize the opportunity to detect a treatment effect of the drug, if there is one in this population.

Age Groups to be Studied:

Pediatric patients ages 1 month (corrected age of at least 44 weeks gestational age) to 24 months, inclusive

Dose Selection:

An age-appropriate dosing regimen for this study must be based on relevant data. Utilizing data available on dosing and tolerability in infants available from previous sponsor initiated trials and literature, the topiramate dose will be titrated up to 5, 15, or 25 mg/kg/day in the double-blind, placebo-controlled phase as discussed in consultation with the Agency. Higher doses, up to 60 mg/kg/day, or the highest tolerated dose, may be explored in the open label extension phase.

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 partial epilepsy 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 (corrected age of at least 44 weeks gestational age) to 24 months, inclusive, 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:

Dosage form: Age-appropriate formulation(s) for younger patients.

Route of administration: Oral

Regimen: To be determined by the development plan

- If the studies you conduct in response to this Written Request demonstrate this drug will benefit children, then an age-appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and testing a new dosage form for which you will seek approval for commercial marketing. If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients.

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  Bioavailability of any formulation used in the studies should be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

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.

STUDY TYPE III: SAFETY

Safety data must be collected in the controlled efficacy trial for the above indication and in an additional pharmacokinetic/tolerability study. Routine safety assessments must be collected at baseline and appropriate follow-up times. i.e. vital signs, weight, height (using a supine stadiometer), clinical laboratory measures, ECGs, and monitoring for adverse events.

Safety concerns deserving special attention include: oligohydrosis (via direct questioning of caregiver/parent and clinical observation), hyperthermia, metabolic acidosis, kidney stones (requiring periodic ultrasound during treatment), hepatotoxicity (baseline LFTs and follow-up testing at end of double blind and multiple timepoints throughout the whole open-label extension, and after discontinuation from the open-label extension) and hyperammonemia (baseline ammonia levels with follow-up testing at end of double-blind phase, at multiple timepoints throughout the whole open-label extension, and after discontinuation from the open-label extension), rash, cognitive/neuropsychiatric adverse events, and effects on growth.

A minimum of 100 patients, age 1 month (corrected age of at least 44 weeks gestational age) to 24 months, inclusive (at enrollment), must be exposed to study drug for one year at effective doses. The long-term safety data must include a significant portion at or above the maximally effective dose shown 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 data on 100 patients followed for at least 1 year with a significant portion of long-term safety data, at doses of $\geq$ 25 mg/kg/day used throughout most of the exposure.

FORMAT OF REPORTS TO BE SUBMITTED

Full study reports 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 study(ies) 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 should be used: Hispanic/Latino or Not Hispanic/Latino.

TlMEFRAME FOR SUBMITTING REPORTS OF THE STUDIES

Reports of the above studies that meet the terms of this Written Request must be submitted to the Agency on or before July 31, 2008 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 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 submission, via fax (30 1-594-0183) 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.

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the

Clinical Trials Data Bank (http://clinicaltrials.gov & http://prsinfo.clinicaltrials.gov/). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site http://prsinfo.clinicaltrials.gov/.

If you have any questions, call Courtney Calder, Pharm.D, Regulatory Project Manager, at 301-796-1050.

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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