DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST

NDA 18-723
NDA 19-680
NDA 20-320
NDA 20-593
NDA 20-782
NDA 21-168
IND 32,231

Abbott Laboratories
Attention: Steven F. Hoff, Ph.D.
Associate Director, Global Pharmaceutical Regulatory Affairs
200 Abbott Park Road
D-491/AP30-1NE
Abbott Park, IL 60064-6157

Dear Dr. Hoff:

Reference is made to your June 22, 2001, Proposed Pediatric Study Request submitted to NDA 21-168 for Depakote ER (divalproex sodium extended-release) Tablets.

To obtain needed pediatric information on valproate (VPA) delivered in various formulations, either as divalproex or valproic acid, 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 in migraine prophylaxis, epilepsy and bipolar disorder. We note that the Agency had previously issued a formal Written Request for these products on August 9, 2002; that request, however, expired on August 9, 2005. The Written Request that follows reflects changes to our original request.

PHARMACOKINETICS

Adequate pharmacokinetic information in pediatric patients may be available in the literature. Literature data can be utilized to calculate age-appropriate dosing regimens for pediatric subjects aged 3-10 years described in this Written Request.

Literature references and/or any unpublished data relevant to the calculation of age-appropriate dosing regimens in subjects ages 3 – 10 years and drug-drug interactions must be provided.

Literature review endpoints:

Valproate pharmacokinetic parameters, such as total steady state Cmax, tmax, t½, apparent volume of distribution (V/F), Cmin, free fraction, and total and free apparent clearance (CL/F) must be provided.

Potential effects of covariates such as age and body-weight (or body-surface area) must be included in the analysis to the extent available from the literature, and used in the dosing recommendations if

deemed appropriate. The potential influence of other covariates, such as concomitant medications, on total apparent clearance (CL/F) must also be investigated to the extent available from the literature.

In particular, the effect of other concomitant antiepileptic drugs on the pharmacokinetics of valproate (and vice versa) must be examined in pediatric patients to the extent available from the literature.

Statistical information:

Descriptive analysis of the pharmacokinetic parameters of valproate. These results will be compared to pharmacokinetic parameters obtained in adults administered divalproex and/or valproic acid (the use of adult historical control data is acceptable).

MIGRAINE PROPHYLAXIS

Type of Study:

Adolescent Efficacy and Safety Study

Objectives/Rationale:

To evaluate the efficacy and short-term safety of divalproex sodium/valproic acid in the prophylactic treatment of migraine headaches in adolescent patients 12 to 17 years of age.

Indication to be Studied:

The use of divalproex sodium/valproic acid for the prophylactic treatment of migraine headache in adolescent patients, ages 12 to 17 years.

Study Design:

Randomized, double-blind, placebo-controlled, parallel group, dose-response, efficacy and short-term safety outpatient study.

Age Groups to be Studied:

Adolescent patients ages 12 to 17 years, inclusive.

Dose Selections:

Age-appropriate dosing regimens for this study will be based on relevant available data.

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

A sufficient number of adolescent migraine patients to be able to detect a clinically and statistically significant difference between treatment and control on a valid measure of migraine prevention. The study will be powered using the effect size observed in the pivotal Depakote ER adult study. The study will also attempt to define an interpretable dose-response relationship in this age group, including the identification of a no-effect dose.

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

Adolescent patients between 12 and 17 years of age, with an average of 3-12 IHS (International Headache Society) defined migraine headaches per 28 days. Enrollment will generally reflect the gender, age, and racial distribution concordant with this patient population. Pregnant patients will be excluded from study enrollment.

Clinical Endpoints:

A single standard measure of migraine attack frequency and measures of clinical safety as defined in the **SAFETY** section.

Drug Information:

Dosage form: oral tablet

Route of administration: oral

Regimen: To be determined by the development program

Statistical Information, Including Statistical Assessments:

Assessment of the between group difference in a standard measure of migraine attack frequency, using an appropriate, prospectively defined statistical methodology, and a descriptive analysis of the safety data.

Labeling That May Result from this Study:

The adolescent migraine efficacy and safety study described in this request may result in the addition to labeling of information pertinent to this study. If Depakote ER is the formulation used in this study, any resulting claims for adolescent patients for Depakote ER could be extended to Depakote Tablets, or vice versa.

PARTIAL SEIZURES

Type of Study:

Pediatric Long-term Safety Study

Objectives/Rationale:

To establish the long-term safety of divalproex sodium/valproic acid in the treatment of partial seizures in pediatric patients ages 3 years to 10 years.

Indication to be Studied:

The use of divalproex sodium/valproic acid for the treatment of partial seizures in pediatric patients, ages 3 to 10 years.

Study Design:

Open-label, multicenter, long-term outpatient safety study.

Age Groups to be Studied:

Pediatric patients ages 3 years to 10 years.

Dose Selection:

An age-appropriate dosing regimen for this study will be based on current divalproex sodium/valproic acid labeling for epilepsy and at investigator's discretion.

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

A sufficient number of pediatric patients with partial seizures to provide data on approximately 50 patients, ages 3 years to 10 years, exposed to study drug for one year.

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

Pediatric patients ages 3 years to 10 years with partial seizures. Enrollment will generally reflect the gender, age, and racial distribution concordant with this patient population.

Clinical Endpoints:

Measures of clinical safety as defined in SAFETY section, in addition to measure of seizure frequency.

Drug Information:

Dosage form: Age-appropriate oral formulation.

Route of administration: Oral

Regimen: Based on current divalproex sodium/valproic acid epilepsy labeling recommendations and at investigator's discretion.

Statistical Information, Including Statistical Assessments:

Descriptive statistics of safety data must be provided.

Labeling That May Result from this Study:

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

ADOLESCENT BIPOLAR DISORDER

General Advice for Developing a Drug for Mania in Adolescent Bipolar Disorder:

According to the DSM IV, the diagnostic criteria for mania are the same for the pediatric and adult population. However, the lower end of the age range for bipolar disorder is not clear. Bipolar disorder below the age of 10 years is considered both uncommon and difficult to diagnose. On the other hand, bipolar disorder in the adolescent population is thought to be relatively common and phenomenologically similar to bipolar disorder seen in adults. Thus, the study of bipolar disorder in adolescents should be feasible and should yield useful information.

Under FDAMA (1997), adequate assessment of adolescents (data sufficient to support a labeling claim) might be based on a single study in pediatric patients, together with confirmatory evidence from another source, perhaps adult data for that disorder. This approach is explicitly considered in the guidance document entitled "Guidance for Industry - Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products". This approach also requires that the adult data be considered reasonably relevant to the course of the disease and the effects of the drug in the pediatric populations.

We believe that a sufficiently strong case has been made for continuity between adult and adolescent bipolar disorder to permit a pediatric claim for a drug already approved in adults for mania to be supported by a single, independent, adequate and well-controlled clinical trial in adolescent mania in association with bipolar disorder. In addition, a pediatric mania program would need to include pharmacokinetic information and safety information in the relevant pediatric age group (but see below, "Safety" and "Pharmacokinetics"). For pediatric mania, we consider the relevant age group to include adolescents aged 10-17 years.

Bibliography

American Psychiatric Association (1994), Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). Washington, DC: American Psychiatric Association.

Type of Study:

Pediatric Efficacy and Safety Study

Objective/Rationale:

The overall goal of the development program would be to establish the safety and efficacy of divalproex sodium/valproic acid in the treatment of adolescent mania in association with bipolar disorder.

Study Design:

For the controlled efficacy study, conduct a randomized, double-blind, parallel group, placebo-controlled acute bipolar disorder trial, with a recommended duration of at least 3 weeks. The trial must allow for early rescue, i.e., treatment with active medication, for patients whose symptoms are not adequately controlled to a specific extent at some point on assigned treatment or who worsen. At least 50% of patients assigned to active drug must complete the trial (i.e. have a Week 4 efficacy evaluation), in order for it to be considered a completed trial. We strongly recommend that the trial be a fixed-dose study including at least two fixed doses of the study drug. Given the lack of a robust

evidence base for the use of divalproex sodium/valproic acid in adolescent mania, there is uncertainty about the optimal therapeutic approach in this population. Thus, this could be a monotherapy trial, or an add-on trial, e.g., adding study drug or placebo to patients already taking lithium.

The trial will be limited to patients capable of giving assent to participate in the trial.

Age Group in Which Studies will be Performed:

Adolescents (ages 10 to 17 years) must be included in the sample. Enrollment will reflect the gender, age, and racial distribution concordant with this patient population. No pregnant patients will be included.

Dose Selection:

An age-appropriate dosing regimen for this study will be based on relevant available data from the medical literature.

Number of Patients to be Studied:

The study must have a sufficient number of patients to provide reasonable statistical power to demonstrate a clinically and statistically meaningful difference between drug and placebo. It should be noted that positive trials in adult mania have generally utilized samples of at least 60 patients per treatment arm. It may be necessary to conduct a multicentered study to ensure a sufficient population accurately diagnosed with mania.

Entry Criteria:

The protocol(s) must include a valid and reliable diagnostic method for recruiting and enrolling adolescents with mania. Given the difficulty in making the diagnosis for screening purposes, it is required that a clinical interview of children and their parents or caregivers be conducted by an adequately trained clinician (e.g. child psychiatrist) to assure accurate diagnosis. It is also required that the diagnosis be confirmed using a reliable and valid semi-structured interview.

Pregnant patients will be excluded from study enrollment.

Patient Evaluations and Study Endpoints:

A scale specific to mania and sensitive to the effects of drug treatment of mania in the target population will be used. A global measure, e.g., the Clinical Global Impression (CGI) may be included. A primary outcome (or outcomes if more than one is considered important) must be prospectively identified for the controlled efficacy trials. This may include “change from baseline to endpoint” on whatever symptom rating scale has been chosen for the trial(s).

Statistical Information:

A detailed statistical plan will be prospectively provided. The trial will be designed with adequate statistical power to detect a reasonable treatment effect (probably best based on typical effects in adults).

Drug Information:

Use age appropriate formulations in the studies described above. Since the pediatric patient population consists of adolescents (ages 10 to 17), your marketed solid dosage formulation may be adequate for these studies.

Labeling that May Result from the Studies:

The pediatric mania efficacy and safety study described in this Written Request may result in the addition to labeling of information pertinent to this study. If Depakote ER is the formulation used in this study, any resulting claims for adolescent patients for Depakote ER could be extended to Depakote Tablets. Likewise, the current claims for adult patients for Depakote Tablets could be extended to Depakote ER.

SAFETY

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

Safety concerns deserving special attention include: hepatotoxicity and hyperammonemia (baseline LFTs and ammonia levels with monthly follow-up testing for 3 months), pancreatitis (baseline amylase levels with monthly follow-up testing for 3 months), thrombocytopenia, rash, cognitive/neuropsychiatric adverse events, and effects on growth.

Cognitive/neuropsychiatric, behavior, and movement assessments must be conducted in an open-label, long-term safety study in migraine prophylaxis, an open-label, long-term safety study in bipolar disorder, and an open-label, long-term safety study in partial seizures. Cognitive/neuropsychiatric assessments using an age-appropriate scale (e.g. Wechsler or Development-Profile II) must be conducted at baseline with periodic testing (e.g. every 6 months). Behavior assessments (e.g. Parent rating scale of the Behavior Assessment System for Children) must be conducted at baseline with periodic testing (e.g. every 6 months). Movement assessments (e.g. movement-related items from the UKU Side Effects Scale) must be conducted at baseline with periodic testing (e.g. every 3 to 6 months).

Because divalproex sodium/valproic acid has recently been developed for partial complex seizures in patients as young as 10 years of age, systematically-collected safety data exists for epilepsy patients 10 to 17 years of age.

For the open-label, long-term safety study in partial seizures, approximately 50 patients, age 3 to 10 years, must be exposed to study drug for one year.

For the study in partial seizures, we have only asked for enrollment of children 3 years of age and older because polytherapy in patients less than 3 years is associated with an elevated risk of hepatic fatality. To meet the terms of this written request, provide the spontaneous U.S. reporting rate of liver failure resulting in death or transplant associated with VPA use for epilepsy in patients 3-10 years of age and 11-17 years of age received during the period of January 1, 2002 up to a date no earlier than 10 months

prior to your complete response to this letter. Additionally, provide these rates after stratifying by VPA monotherapy and VPA use in combination with other antiepileptic medications.

For the migraine indication, a sufficient number of adolescent migraine patients, between 12 and 17 years of age, to be able to characterize the long-term safety of divalproex sodium/valproic acid when used to prevent migraine attacks over one year must be assessed. Enrollment must be adequate to obtain well-characterized safety data at clinically relevant doses from approximately 150 subjects in the relevant populations treated for 6 months and approximately 75 subjects treated for one year.

For the adolescent bipolar disorder indication, a sufficient number of adolescent patients, ages 10 to 17 years, to be able to characterize the long-term safety of divalproex sodium/valproic acid when used as monotherapy or adjunctive therapy (with divalproex sodium/valproic acid) to treat adolescent mania in association with bipolar disorder must be enrolled to ensure that approximately 100 patients will be exposed to study drug for at least six months.

FORMAT OF REPORTS TO BE SUMBITTED

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 studies should 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.

TIMEFRAME FOR SUBMITTING REPORTS OF THE STUDIES

Reports of the above studies must be submitted to the Agency on or before October 7, 2007. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the 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.

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. 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 should be submitted as a New Drug Application (NDA) or as a supplement to your 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 (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 should 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

1/31/2006 07:08:45 PM