

HFD-104

Murphy

APR 28 1999

NDA 20-151
NDA 20-699

Wyeth-Ayerst Laboratories
Attention: Roy J. Baranello, Jr.
Director, Regulatory Affairs
P.O. Box 8299
Philadelphia, Pennsylvania 19101-1245

Three Years from
The Date of this Letter APR 28 2002

Dear Mr. Baranello:

Reference is made to your Proposed Pediatric Study Request submitted on December 30, 1998, under IND 41,412 for Effexor XR (venlafaxine Hydrochloride) Extended-Release 37.5 mg, 75 mg, 100 mg, and 150 mg Capsules.

We have completed our review of your submission and concluded that your proposed pediatric study request is incomplete.

To obtain needed pediatric information on venlafaxine, 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 trials in pediatric patients with depression and Generalized Anxiety Disorder (GAD) described below.

PEDIATRIC DEPRESSION

Background Comments on Pediatric Depression

Under current regulations [21 CFR 201.57(f)(9)(iv)], a new claim in a pediatric population could be established by extrapolating the effectiveness results of adequate and well controlled studies in adults for the same entity if it were believed that depression was essentially the same disease in adults and children. Under FDAMA (1997), a claim might be based on a single study in pediatric patients along with confirmatory evidence from another source, perhaps adult data for that disorder, an approach considered in the draft guidance document entitled "Guidance for Industry - Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products". This approach too requires some degree of belief that the course of the disease and the effects of the drug are sufficiently similar in the pediatric and adult populations to make data from the adult efficacy studies pertinent to pediatric patients. Unfortunately, in our view there is little reason to assume continuity between adult and pediatric depression and our concern about the extrapolability of adult depression data to pediatric depression is more than theoretical. While we, of course, acknowledge the one published positive report of fluoxetine in pediatric depression (Emslie, et al, 1997), we are concerned about the preponderance of negative studies

of antidepressants in pediatric populations. We recognize that all of these negative studies utilized tricyclic antidepressants, and that, in addition, there are other possible explanations for the negative outcomes, e.g., sample size, entry criteria, outcome measures, etc. Nevertheless, these negative trials (at least 12 in number) lead to a substantial concern about the ability to extrapolate positive antidepressant findings from adult to pediatric patients. Consequently, we believe that a pediatric depression claim for any antidepressant already approved in adult depression would need to be supported by two independent, adequate and well controlled clinical trials in pediatric depression. In addition, a pediatric depression program would need to include pharmacokinetic information and safety information in the relevant pediatric age groups. For pediatric depression, we consider the relevant age groups to include children (ages 7 through 11) and adolescents (ages 12 through 17).

Specific Study Requirements for Development Program in Pediatric Depression

Types of Studies

1. Pediatric Efficacy and Safety Studies
2. Pediatric Pharmacokinetic Study
3. Pediatric Safety Study

Objective/Rationale

The overall goal of the development program is to establish the safety and efficacy of the study drug in the treatment of pediatric depression, and to develop other information, e.g., pharmacokinetic, pertinent to using the drug in the pediatric population.

Study Design

Pediatric Efficacy and Safety Studies

- For the controlled efficacy studies, conduct two randomized, double-blind, parallel group, placebo-controlled acute treatment trial, with a recommended duration of at least 6 to 8 weeks. We recommend that at least one of the two studies should be a fixed dose study including two or more fixed doses of the study drug. You may consider dosing patients on the basis of patient weight. Randomization must be stratified by the two age groups studied. Ideally, a relapse prevention trial would follow from the acute treatment trials, involving the randomization of responders from the acute treatment trials to continuation on either study drug or placebo, with follow-up observation for relapse for a period of 6 months or more. Please note that a relapse prevention trial is not required under this written request.

Pediatric Pharmacokinetic Study

- A pharmacokinetic study to provide information pertinent to dosing of the study drug in the relevant pediatric population. These data could come from traditional pharmacokinetic studies, or alternatively, from population kinetic approaches applied to controlled efficacy trials or to other safety trials. You should be aware that a guidance document on population pharmacokinetic studies is available under [www.fda.gov/cder/guidance/1852fnl.pdf].

Pediatric Safety Study

- Safety data should be collected in the controlled efficacy trials. Longer-term safety data should be generated in longer-term open extensions from these trials and/or in separate longer-term open safety studies.

Age Group in Which Study(ies) will be Performed – All Studies

Both children (ages 7 to 11) and adolescents (ages 12 to 17) should be equally represented in the samples, and there should be a reasonable distribution of both sexes in these strata.

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

Pediatric Efficacy and Safety Studies

- While it is difficult to specify the sample size needed to show a difference between drug and placebo in this population, it should be noted that, in the only published positive antidepressant trial in pediatric depression (Emslie, et al, 1997), there were 48 patients in each of the two treatment arms.

Pediatric Pharmacokinetic Study

- A sufficient number of subjects to adequately characterize the pharmacokinetics in the above age groups.

Pediatric Safety Study

- A sufficient number of pediatric patients to adequately characterize the safety of venlafaxine at clinically effective doses for a sufficient duration.

Entry Criteria

The protocols should include a valid and reliable diagnostic method for recruiting children and adolescents with major depressive disorder.

Study Endpoints

Pediatric Efficacy and Safety Studies

- It is essential to identify a single primary outcome for the controlled efficacy trials, and ordinarily this should be change from baseline to endpoint on whatever symptom rating scale you have chosen for your trials.

Pediatric Pharmacokinetic Study

- Pharmacokinetic measurements as appropriate.

Pediatric Safety Study

- Appropriately frequent standard measures of safety (clinical - including signs and symptoms and laboratory).

Statistical Information

Pediatric Efficacy and Safety Studies

- These trials should have a detailed statistical plan. Ordinarily these trials should be designed with at least 80% statistical power to detect a treatment effect of conventional ($p=0.05$) statistical significance.

Pediatric Pharmacokinetic Study

- Descriptive analysis of the pharmacokinetic parameters.

Pediatric Safety Study

- Descriptive analysis of the safety data.

Study Evaluations

Pediatric Efficacy and Safety Studies

- A scale specific to pediatric depression and sensitive to the effects of drug treatment of pediatric depression, e.g., the Children's Depression Rating Scale—Revised, and a global measure, e.g., the Clinical Global Impression (CGI).

Pediatric Pharmacokinetic Study

- The pharmacokinetic assessments should be made with respect to the study drug and any metabolites that make substantial contributions to its efficacy and/or toxicity. For the parent and each metabolite followed, the data collected should provide estimates of the pharmacokinetic parameters including AUC, half-life, C_{max} , t_{max} , and apparent oral clearance in pediatric subjects in the relevant age range. You should be aware that a draft guidance document on pediatric pharmacokinetic studies is available under [www.fda.gov/cder/guidance/index.htm], under Clinical/Pharmacological (Draft)].

Pediatric Safety Study

- Routine safety assessments should include vital signs, weight, clinical laboratory, ECGs, and monitoring for adverse events. Although not a part of this Written Request, we remind you that it may be important to determine the effect of the study drug on the growth and development of pediatric patients, and we encourage you to consider longer-term studies of a year or more to address this question if the acute studies demonstrate antidepressant activity.

Drug Information

Use age appropriate formulations in the studies described above. Since the pediatric patient population consists of both children (ages 7 to 11) and adolescents (ages 12 to 17), your marketed solid dosage formulation should be adequate for these studies.

Drug Concerns

No specific concerns related to administration to pediatric patients were identified while studying venlafaxine in adults, nor have specific concerns been identified during the postmarketing experience.

PEDIATRIC GENERALIZED ANXIETY DISORDER (GAD)**Background Comments on Pediatric GAD**

Under current regulations [21 CFR 201.57(f)(9)(iv)], a new claim in a pediatric population could be established by extrapolating the effectiveness results of adequate and well controlled studies in adults for the same entity if it were believed that GAD was essentially the same disease in adults and children. Under FDAMA (1997), a claim might be based on a single study in pediatric patients along with confirmatory evidence from another source, perhaps adult data for that disorder, and approach considered in the draft guidance document entitled "Guidance for Industry - Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products". This approach too requires some degree of belief that the course of the disease and the effects of the drug are sufficiently similar in the pediatric and adult populations to make data from the adult efficacy studies pertinent to pediatric patients. Despite the fact that some experts in child psychiatry view GAD as essentially the same disorder in adults and children, a view that is legitimized to some extent by the inclusion of the GAD diagnosis for pediatric patients in DSM-IV, there remains some question regarding whether or not GAD can be considered the same disorder in adults and children. A major difficulty is that there is no experience from adequate and well-controlled trials of venlafaxine or, in fact, any other psychotropic agents in pediatric GAD upon which to draw any reassurance that this is a reasonable extrapolation. For the reasons outlined above, we believe that an extension of the claim for venlafaxine in GAD into pediatric patients with this diagnosis should be supported by positive results from two, independent, adequate and well-controlled clinical trials.

Specific Study Requirements for Development Program in Pediatric GAD**Types of Studies**

Pediatric Efficacy and Safety Studies
Pediatric Pharmacokinetic Study
Pediatric Safety Study

Objective/Rationale

The objective will be to determine the safety and efficacy of venlafaxine relative to placebo in the treatment of children and adolescents with GAD.

Study Design

Pediatric Efficacy and Safety Studies

- The design of these studies must be randomized, double blind, placebo controlled, parallel group studies. We recommend that at least one of the two studies include treatment arms with two or more fixed doses of venlafaxine. You may wish to consider dosages based upon the weight of the subject. The studies must be at least 4-6 weeks of duration to measure a meaningful clinical change in the disorder.

Pediatric Pharmacokinetic Study

- In addition, there would need to be pharmacokinetic data to provide information pertinent to dosing of the study drug in the relevant pediatric population. These data could come from traditional pharmacokinetic studies, or alternatively, from population kinetic approaches applied to controlled efficacy trials or from other safety trials. Please refer to the previous paragraph under "Specific Study Requirements for Development Program in Pediatric Depression".

Pediatric Safety Study

- Safety data could come from controlled efficacy trials. Longer-term safety data should be generated in longer-term open extensions from these trials and/or in separate longer-term open safety studies. Safety data will also be available, of course, from the pediatric depression studies.

Age Group in Which Study(ies) will be Performed – All Studies

An age range of 6-17 years, give or take a year or two, is acceptable. The studies should include subjects from the entire age range.

Number of Patients to be Studied or Power of Study to be Achieved**Pediatric Efficacy and Safety Studies**

- To be determined based on your choice of outcome measure.

Pediatric Pharmacokinetic Study

- A sufficient number of subjects to adequately characterize the pharmacokinetics in the above age groups.

Pediatric Safety Study

- A sufficient number of pediatric patients to adequately characterize the safety of venlafaxine at clinically effective doses for a sufficient duration.

Entry Criteria

The entry criteria should include a reliable and valid diagnostic method for identifying children and adolescents with GAD. As the diagnosis of GAD in this age group was established only a few years ago under DSM-IV, it would be desirable for you to provide the Agency with data supporting the validity of the chosen diagnostic method. The entry criteria should also include a method for determining and handling comorbid diagnoses.

Study Endpoints**Pediatric Efficacy and Safety Studies**

- The clinical endpoint chosen should be one that is expected to be sensitive to the effects of a drug on the symptoms of GAD. It should also be specific to the assessment of the manifestations of GAD and validated for that purpose.

Pediatric Pharmacokinetic Study

- Pharmacokinetic measurements as appropriate.

Pediatric Safety Study

- Appropriately frequent standard measures of safety (clinical - including signs and symptoms and laboratory).

Statistical Information**Pediatric Efficacy and Safety Studies**

- It is essential to identify a single primary outcome for the controlled efficacy trials, and ordinarily this should be change from baseline to endpoint on whatever symptom rating scale you have chosen for your trial. This trial should have a detailed statistical plan. Ordinarily this trial should be designed with at least 80% statistical power to detect a treatment effect of conventional ($p=0.05$) statistical significance.

Pediatric Pharmacokinetic Study

- Descriptive analysis of the pharmacokinetic parameters.

Pediatric Safety Study

- Descriptive analysis of the safety data.

Study Evaluations**Pediatric Efficacy and Safety Studies**

- The efficacy assessments should include a validated symptom rating scale specific to pediatric GAD and expected to be sensitive to the effects of drug treatment of pediatric GAD, and a global measure, e.g., the Clinical Global Impression (CGI).

Pediatric Pharmacokinetic Study

- The pharmacokinetic assessments should be made with respect to the study drug and any metabolites that make substantial contributions to its efficacy and/or toxicity. For the parent and each metabolite followed, the data collected should provide estimates of the pharmacokinetic parameters including AUC, half-life, C_{max} , t_{max} , and apparent oral clearance in pediatric subjects in the relevant age range. You should be aware that a draft guidance document on pediatric pharmacokinetic studies is available under [www.fda.gov/cder/guidance/index.htm, under Clinical/Pharmacological (Draft)].

Pediatric Safety Study

- Routine safety assessments should include vital signs, weight, clinical laboratory, ECGs, and monitoring for adverse events. Although not a part of this Written Request, we remind you that it may be important to determine the effect of the study drug on the growth and development of pediatric patients, and we encourage you to consider longer-term studies of a year or more to address this question if the acute studies demonstrate activity in pediatric GAD.

Drug Information

Use age appropriate formulations in the studies described above. Since the pediatric patient population consists of an age range of 6 – 17 years old, your marketed solid dosage formulation should be adequate for these studies.

Drug Concerns

No specific concerns related to administration to pediatric patients were identified while studying venlafaxine in adults, nor have specific concerns been identified during the postmarketing experience.

Labeling That May Result from the Studies

The pediatric depression efficacy, safety, and pharmacokinetic studies described in this request could result in the addition to labeling of information pertinent to these studies. Similarly, the data generated from the GAD efficacy, safety, and pharmacokinetic studies described in this request could result in the addition to labeling of information pertinent to these studies.

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.

Timeframe for Submitting Reports of the Study(ies)

Reports of the above studies must be submitted to the Agency within 3 years from the date of this letter to be eligible to qualify for pediatric exclusivity extension under Section 505A of the Act. Please remember that pediatric exclusivity extends only existing patent protection or exclusivity that has not expired at the time you submit your reports of studies in response to this Written Request.

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. We recommend you seek a written agreement with FDA before developing pediatric studies. 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 should be submitted 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,

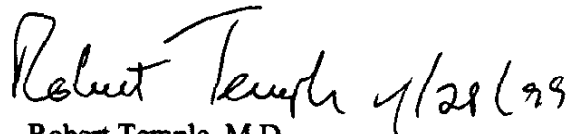
via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

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.

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 to the pediatric population.

If you have any questions, contact Paul A. David, Regulatory Project Manager, at (301) 594-5530.

Sincerely yours,



Robert Temple, M.D.

Director

Office of Drug Evaluation I

Center for Drug Evaluation and Research

cc:

Archival NDA 20-699

Archival NDA 20-151

HFD-120/division file

HFD-120/PDavid

HFD-120/RKatz/TLaughren/AMosholder/RGlass/GDubitsky

HFD-100/RTemple

HFD-600/Office of Generic Drugs

HFD-2/MLumpkin

HFD-104/DMurphy

HFD-6/KRoberts

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Final:04/22/99pd

filename: EFFEXORPEDS02.DOC

PEDIATRIC WRITTEN REQUEST LETTER
INFORMATION REQUEST (IR)