DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022567 **WRITTEN REQUEST**

Forest Laboratories, Inc.
Attention: Kaity Posada, Pharm.D.
Director, Regulatory Affairs
Harborside Financial Center, Plaza V
Jersey City, NJ 07311

Dear Dr. Posada:

Please refer to your new drug application (NDA) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Viibryd (vilazodone) oral tablets.

Reference is made to your Proposed Pediatric Study Request submitted to IND 54,613 for Viibryd (vilazodone) oral tablets on January 30, 2012, requesting issuance of a Written Request to conduct pediatric studies to qualify for exclusivity under section 505A of the Act.

To obtain needed pediatric information on vilazodone, 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), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from trials in pediatric patients with Major Depressive Disorder (MDD) as described below.

PEDIATRIC MAJOR DEPRESSIVE DISORDER

General Advice for Developing a Drug for Pediatric Major Depressive Disorder

Major Depressive Disorder (MDD) is a major public health problem in children and adolescents. MDD can be a severe, debilitating, and potentially life-threatening medical condition that can significantly impair family, psychosocial, and academic functioning. It is often a recurrent and chronic disorder. In addition, MDD is associated with suicide. The estimated lifetime prevalence of MDD in children and adolescents is 3.3% to 3.7%.

Under current regulations [21 CFR 201.57(f)(9)(iv) in the 2008 CFR], 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 FDAAA (2007), 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with confirmatory evidence from another source, perhaps adult data for that disorder, an approach considered in the draft guidance document entitled "Guidance for Industry- Providing Clinical Evidence of Effectiveness for Human Drug and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 also 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. At the present time, however, there are insufficient data to support reliance on studies in adults with major depressive disorder to support an indication in pediatrics. Our concern about the extrapolability of data from adults with MDD to pediatric patients with MDD is more than theoretical. While we acknowledge that fluoxetine and escitalopram have been demonstrated to be effective in treating MDD in pediatric patients, other antidepressant drugs have not been reliably demonstrated to be of benefit in treating pediatric MDD. Negative results have been observed not only for the older antidepressants, i.e., tricyclic antidepressants, but also for the current generation of antidepressants, with the exception of fluoxetine and escitalopram. Although we recognize that there are many possible explanations for these negative studies, they, nevertheless, lead to a substantial concern about the ability to extrapolate positive antidepressant findings from adult to pediatric patients. Consequently, adequate evaluation of the effect of an antidepressant in pediatric major depressive disorder, even for an antidepressant already approved in adult major depressive disorder, will require two independent, adequate and well controlled clinical trials in pediatric patients, in addition to pharmacokinetic and safety information in the relevant pediatric age groups. For pediatric major depressive disorder, we consider the relevant age groups to include children (ages 7 through 11) and adolescents (ages 12 through 17).

The inclusion of a placebo control group is scientifically necessary; neither the safety nor the efficacy data would not be interpretable without a placebo control group. The inclusion of a placebo group is, therefore, ethically acceptable. If the studies could not provide meaningful safety and efficacy data, it could be difficult to justify exposing pediatric patients to the study drug. (Refer to ICH-E10 guidelines: Choice of Control Group and Related Issues in Clinical Trials). In addition, patients in the placebo and active drug groups would be discontinued from the study if they had an exacerbation of illness that required definitive treatment. Also, high risk patients (e.g., at risk for suicide or with unstable illness) would be excluded from the study. Furthermore, patients in the placebo and active drug groups would be permitted to receive concomitant non-pharmacologic treatments during the course of the studies.

Specific Study Requirements for a Development Program in Pediatric Major Depressive Disorder

Overall Objectives/Rationale

The overall objectives of the pediatric development plan are to establish the safety and efficacy of treatment with vilazodone on the core symptoms of MDD in children and adolescents. This will require the development of other information, including pharmacokinetic data, to support dosing recommendations in pediatric patients.

Required Studies:

- Nonclinical Toxicology Study
- Pharmacokinetic Studies

- Pediatric (ages 12-17 years) Efficacy and Safety Study
- Pediatric (ages 7-17 years) Efficacy and Safety Study
- Pediatric (ages 7-17 years) Safety Study

Study Design

Nonclinical study:

Based on review of the non-clinical toxicology data that have already been submitted, the following study must be conducted prior to enrollment of children (less than 12 years of age) into the clinical studies described in this written request. To support the use of vilazodone in children less than 12 years of age, you must conduct a study to assess the safety of vilazodone in juvenile rats. This study must include evaluation of neurological/behavioral development and reproductive development. The final report for this study must be submitted prior to enrollment of children less than 12 years of age into repeated-dose clinical studies. We acknowledge that you have submitted a protocol for this study (12/29/2011) and that we have provided you with our comments (1/31/2012).

Pharmacokinetic Studies:

Given the pharmacokinetic data already available for this drug, you are not required to conduct a dedicated pediatric pharmacokinetic (PK) study. You must, however, obtain pharmacokinetic data in the pediatric MDD efficacy and safety studies (Study 1 and Study 2 described below). Based on pharmacokinetic modeling and simulation using dose-response and PK data in adults (submitted previously to the NDA), the doses for adolescents (ages 12 to 17 years) can be selected to match exposures in adults. The selected doses must be agreed upon by the Agency. Using these doses, you must first conduct a fixed-dose, efficacy and safety study in adolescent patients (ages 12 to17 years) with MDD. This study must incorporate sparse PK sampling for further characterizing pharmacokinetics in adolescents, in addition to assessing dose-response relationships. The results of the first study will guide the selection of doses for the second efficacy and safety study, which will use flexible dosing and sparse PK sampling in children and adolescents (7 to 17 years of age). The selected doses must be agreed upon by the Agency. Vilazodone pharmacokinetics in children and adolescent patients can be characterized via a population PK approach using data from the two efficacy and safety studies.

Study 1 – Adolescent Efficacy and Safety Study:

You must conduct a randomized, double-blind, placebo-controlled, parallel-group, short-term, fixed-dose efficacy and safety study of vilazodone in the treatment of pediatric patients (ages 12 to 17 years) with a diagnosis of MDD (as defined by Diagnostic and Statistical Manual of Mental Disorders-IV-TR criteria). The study must assess at least 2 fixed doses. The selected doses must be agreed upon by the Agency. The fixed-dose design is necessary for assessing potential dose-response relationships for efficacy and safety and to determine the lowest effective dose.

Study 2 – Child and Adolescent Efficacy and Safety Study:

You must conduct a randomized, double-blind, placebo-controlled, parallel-group, short-term, fixed-dose or flexible-dose, efficacy and safety study of vilazodone in the treatment of children and adolescent patients (ages 7 to 17 years) with a diagnosis of major depressive disorder. You must use the pharmacokinetic results from the adolescent study to guide the selection of doses for this study in children and adolescents.

Study 3 – Long-term Safety Study:

You must collect longer-term safety data for a minimum duration of 6 months of exposure to vilazodone in pediatric patients (ages 7 to 17 years) with a diagnosis of MDD. The longer-term safety data could be obtained from open-label studies, e.g., a longer-term open-label extension of the controlled efficacy studies, or from separate longer-term open-label safety studies. The long-term safety data must be from doses at or above the dose or doses identified as effective in an adequately designed efficacy trial, as described above. If an adequately designed and conducted efficacy trial fails to detect a drug effect, you must still collect long-term safety data at doses equal to the adult exposure of the drug.

Studies 1, 2, and 3 must allow for early discontinuation from the studies for patients whose symptoms worsen or are not adequately controlled on assigned treatment. At least 50% of patients assigned to active drug must complete to the nominal endpoint of these studies in order for the studies to be considered a completed trial and, therefore, responsive to this request. You must collect and provide complete information for the reasons patients discontinue from the studies.

Age Group in which the Studies will be Conducted

Study 1: Adolescents (ages 12 to 17 years).

Study 2 and Study 3: Children (ages 7 to 11 years) and adolescents (ages 12 to 17 years) must be approximately evenly distributed over the age range in the study. You should make every attempt to have at least 40% of subjects in the age group 7 to 11 years in these two studies.

In all 3 studies, the numbers of male and female patients should be approximately equal within these samples.

Number of Patients to be Studied

Study 1 and Study 2 must include a sufficient number of patients to provide 85% statistical power to demonstrate a clinically meaningful difference between drug and placebo. It may be difficult to specify the required sample size to accomplish this; however, positive trials in pediatric MDD have generally utilized sample sizes of about 100 patients per treatment arm. It

may be necessary to conduct an interim analysis to estimate variance late in the study to readjust the sample size to ensure that the study has adequate power (see Statistical Information).

The safety study must include at least 100 patients exposed to vilazodone for at least 6 months.

These studies must include reasonable representation of ethnic and racial minorities. The proportions of these groups in the studies should reasonably reflect proportions in the disease population. If you are not able to enroll adequate numbers of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

Entry Criteria

The studies must include a valid and reliable diagnostic method for recruiting and enrolling children and adolescents meeting DSM-IV criteria for MDD. Given the difficulty in making the diagnosis for screening purposes, a clinical interview of pediatric patients and their caregivers must be conducted by an adequately trained clinician (e.g., a child psychiatrist or other clinician adequately trained to conduct such interviews) to assure accurate diagnosis. The diagnosis must be confirmed using a reliable and valid semi-structured interview.

Study Endpoints

Pharmacokinetic Endpoints

Pharmacokinetic assessments must be conducted with respect to vilazodone and any metabolites that make substantial contributions to its efficacy and/or toxicity. For the parent and each metabolite measured, the data collected must provide estimates of important pharmacokinetic parameters, e.g., 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 at [www.fda.gov/cder/guidance/index.htm, under Clinical/Pharmacological (Draft)].

The pharmacokinetic endpoints for vilazodone must include clearance and volume of distribution. The study must be prospectively powered to target a 95% CI [confidence interval] within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for vilazodone, with at least 80% power. A summary (mean, median) of pharmacokinetic parameters such as half-life must also be reported.

Efficacy Endpoints

You must use a scale specific to pediatric MDD and sensitive to the effects of drug treatment of MDD in the target population, e.g., the Children's Depression Rating Scale-Revised (CDRS-R). It is essential to identify a primary outcome (or outcomes, if more than one is considered important) for the controlled efficacy trials; ordinarily this would be the change from baseline to endpoint on the symptom rating scale you have chosen for the studies.

Safety Endpoints

You must perform routine safety assessments at baseline and at appropriate follow-up time points in all 3 studies. The assessments must include physical examination, vital signs (pulse rate and blood pressure), weight, height (as measured by stadiometer), clinical laboratory measures (chemistry, including liver function tests and bilirubin; hematology; glucose; serum lipids; and urinalysis), ECG, and monitoring for adverse events, including suicidal ideation and suicidal behavior.

Suicidality Assessments in Clinical Studies

There has been much focus on treatment-emergent suicidality (suicidal ideation and behavior) in recent years, including the question of how best to assess for this in future trials. Given this development, the Division of Psychiatry Products (DPP) has developed a policy regarding how we will address this issue. All clinical protocols for products developed in DPP, whatever the indication, must include a prospective assessment for suicidality. These assessments must be included in every clinical protocol, at every planned visit, and in every phase of development. An acceptable instrument would be one that maps to the Columbia Classification Algorithm for Suicide Assessment (C-CASA). The Columbia Suicide Severity Rating Scale (C-SSRS) would be an acceptable instrument. You can obtain information about the C-SSRS at http://www.cssrs.columbia.edu. You may propose alternatives, but you would then need to justify that the alternative instrument would meet this need, and you would need to obtain DPP's prior approval of the instrument. There will likely be several different approaches to administering the C-SSRS, including investigator administered or self report (phone, computer, etc). Any approach could be acceptable as long as the method is validated.

There are two reasons for implementing this policy. One is to ensure that we collect better data on suicidality than we have up to now, so that in the future we will be able to conduct additional meta-analyses on this matter. A second reason is to ensure that patients in clinical trials who are experiencing suicidality are detected and adequately managed. This is important whether or not a particular drug is associated with treatment-emergent suicidality.

Data Monitoring Committee

A Data Monitoring Committee (DMC) must be included for the following reasons:

1. There is an increased risk of suicidal ideation and suicidal behavior in children and adolescents treated with antidepressants.
2. The studies will be conducted in children, a potentially fragile population.
3. These will be large, multicenter studies of relatively long duration.

See Guidance: *Establishment and Operation of Clinical Trial Data Monitoring Committees,*
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf

Statistical Information (Including Power of Studies and Statistical Assessments)

Pharmacokinetic Endpoints and Analysis in Efficacy and Safety Studies

You must perform a descriptive analysis of the pharmacokinetic parameters described above.

Efficacy Analysis in the Efficacy and Safety Studies

The studies must have a detailed statistical plan. A preliminary statistical analysis plan must be submitted for comment prior to initiating the efficacy and safety study, and you must obtain agreement on the final statistical plan prior to 25% enrollment.

The studies must be designed with at least 85% statistical power to detect a clinically meaningful treatment effect (probably best based on typical effects in adults) at a Type I error rate of 5% (two-sided). You must obtain agreement with the Division with regard to the treatment effect prior to initiating the study. For the purpose of satisfying the Written Request, this treatment effect might, for example, be defined as a 4 unit difference between drug and placebo in the change from baseline in the Children Depression Rating Scale (CDRS) total score. The sample size calculation should address the potential loss of power due to the expected rate and pattern of missing observations

To ensure that the studies are adequately powered, you must obtain an estimate of variability from an interim analysis, and then follow a pre-specified rule to adjust the sample size to achieve the specified target power. This interim analysis must be performed when the study is close to finishing (for example, at > 90% of the initially planned enrollment). You may estimate the variability based on a blinded and pooled analysis of all groups, in which case no alpha-spending adjustment is required for this interim analysis. If, however, you want to perform an efficacy assessment at this or some other interim analysis, an appropriate alpha adjustment would be required.

Safety Study

You must provide descriptive analyses of the safety data.

GENERAL REQUIREMENTS AND COMMENTS

Drug Information (Dosage Form, Route of Administration, Regimen)

- *Dosage form: tablet.*
- *Route of administration: oral.*
- *Regimen: once daily.*

Use an age-appropriate formulation in the studies described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation

and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

In accordance with section 505A(e)(2), if

1. you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);

2. the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and

3. you have not marketed the formulation within one year after the Agency publishes such notice,

The Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

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. Under these circumstances, 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 labeling 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 must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

Known Drug Safety Concerns and Monitoring

In each of the pediatric studies, you must adequately assess the following safety concerns that were identified in the adult MDD vilazodone program: nausea, vomiting, decreased appetite, and weight loss.

Extraordinary Results

In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the

requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

Labeling That May Result from the Studies

You must submit proposed pediatric labeling to incorporate the findings of the studies. Under section 505A(j) of the Act, regardless of whether the studies demonstrate that vilazodone is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the studies. Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the studies.

Format and Types of Reports to be Submitted

You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must 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, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072349.pdf.

Timeframe for Submitting Reports of the Studies

Reports of the above studies must be submitted to the Agency on or before June 30, 2018. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

Response to Written Request

Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the studies. If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the studies, but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

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.

Reports of the studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are 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 to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, complete response); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872

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.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, call Bill Bender, Regulatory Project Manager, at 301-796-2145.

Sincerely,

{See appended electronic signature page}

Ellis Unger, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

ELLIS F UNGER
11/20/2012