DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021487, 021627, 022525
IND 073075

REVISED WRITTEN REQUEST
AMENDMENT 1

Forest Research Institute
A Subsidiary of Forest Laboratories, Inc
Attention: Kathleen Waldron, MBA
Associate Director, Regulatory Affairs
Harborside Financial Center
Plaza V, 24th Floor, Room 50
Jersey City, NJ 07311

Dear Ms. Waldron:

Please refer to your correspondence dated October 22, 2012, requesting changes to FDA's January 25, 2012, Written Request for pediatric studies for NAMENDA (memantine hydrochloride).

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on January 25, 2012, remain the same. (Text added is underlined. Text deleted is strikethrough.)

Number of Patients to Be Studied

Pediatric Efficacy and Safety Studies

The studies must have sufficient numbers of subjects to provide at least 85% statistical power to detect a clinically meaningful treatment benefit on an acceptable primary endpoint. The Social Responsiveness Scale (SRS) total score would be acceptable as the primary efficacy measure. If you choose to use change from baseline in SRS total score as the primary endpoint for your short-term, randomized, double-blind, parallel group study, the trial must be powered to show a ten-unit difference between drug and placebo. For your randomized withdrawal study, your statistical analysis plan must explain how you intend to demonstrate and ensure 85% statistical power. To ensure adequate statistical power in these studies, you must conduct interim analyses ~~to estimate variance~~ late in the trials for a ~~and increase the~~ sample size increase if necessary (see Statistical Information).

Statistical Information, Including Power of Study(ies) and Statistical Assessments

Pediatric Efficacy Studies

These trials must each have a detailed statistical plan. The trials must be designed with at least 85% statistical power to detect a clinically meaningful treatment effect at conventional levels (alpha=0.05, 2-tailed) of statistical significance. For your randomized withdrawal trial, a preliminary statistical analysis plan must be submitted for comment prior to initiating this trial, and you must obtain agreement on the final statistical plan prior to ~~25%~~ 45% enrollment. ~~Your studies must be powered to be able to detect a clinically meaningful treatment benefit on the primary endpoint. For the purpose of satisfying the Written Request, a clinically meaningful treatment benefit for the short-term study must be defined as a 10 unit difference between drug and placebo in change from baseline to endpoint on the Social Responsiveness Scale total score. This requires you to show that, if the true treatment effect for one of the treatment groups was minimally clinically meaningful, the pre-planned analysis would have at least 85% power to infer that the memantine group is significantly different from placebo. You may consider obtaining an estimate of variability to use in power calculations from a preliminary study~~ Unless the initial sample size is convincingly large, the statistical analysis plan must include a plan for an interim analysis, to ensure adequate power for this study.

For the randomized, double-blind, parallel group, 12-week study, a clinically meaningful treatment benefit must be defined as a 10 unit difference between drug and placebo in change from baseline to endpoint on the SRS total score. You must conduct a blinded interim analysis to estimate the variance for potential sample size increase. ~~However, to ensure that the studies are adequately powered, you must obtain estimates of variability from~~ Any interim analyses ~~and then follow a~~ for the studies must be pre-specified ~~rule~~ and you must follow the pre-specified rules to adjust the sample size to achieve the specified target power. ~~These~~ Such an interim ~~analyses~~ analysis must be performed by an independent third party when the studies are close to finishing (for example, at >90% of initially planned enrollment). ~~Options for estimating variability are (1) a blinded, pooled analysis of all groups, or (2) a partially unblinded analysis of variability within each group (performed by an independent third party). No alpha-spending adjustment is required for this interim analysis to assess the variability, but if you want to perform an efficacy assessment at this or some other interim analysis, an appropriate alpha adjustment is required. For the randomized withdrawal study, you must propose an endpoint, a clinically meaningful benefit for that endpoint, and an analysis plan, including a plan for an interim look, to ensure adequate power for this study. The Agency must concur with these study design elements before you proceed with the study.~~

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated January 25, 2012, as amended by this letter must be submitted to the Agency on or before December 7, 2014, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies 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, 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. In addition, send a copy of the cover letter of your submission, via fax (240-276-9327) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, contact CDR Kofi Ansah, Pharm.D., Senior Regulatory Project Manager, at (301)796-4158 or email: Kofi.Ansah@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Complete Copy of Written Request as Amended

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

REVISED WRITTEN REQUEST – AMENDMENT #1

NDA 021487, 021627, 022525

Forest Research Institute
A Subsidiary of Forest Laboratories, Inc.
ATTENTION: Kathleen Waldron
Associate Director, Regulatory Affairs
Harborside Financial Center
Plaza V, 24th Floor, Room 50
Jersey City, NJ 07311

Dear Ms. Waldron:

Reference is made to your July 7, 2011, Proposed Pediatric Study Request for NAMENDA (memantine hydrochloride) submitted to your IND 73075.

Reference is also made to your approved new drugs applications for Namenda: NDA 021487 Namenda (memantine hydrochloride) tablets, NDA 021627 Namenda (memantine hydrochloride) oral solution, and NDA 22525 Namenda XR (memantine hydrochloride extended-release) capsules.

BACKGROUND:

These studies would investigate the potential use of memantine HCl, an N-methyl-D-aspartate (NMDA) receptor antagonist, for the treatment of the core social impairment symptoms in subjects (6-12 years) with autism or autism spectrum disorder (ASD).

Memantine HCI currently is approved for the treatment of moderate to severe dementia of the Alzheimer's type (DAT) under the tradename Namenda.

Autism (Autistic Disorder) and Autism Spectrum Disorder (ASD):

Autism is a neuro-developmental disorder characterized by impairments in social interactions, communication, and restricted interests as well as stereotyped behaviors. Autistic disorder, or "classic" autism, is a more severe type of autistic spectrum disorder (ASD) which includes Autistic Disorder, Asperger's syndrome, and Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS)[1].

In autistic disorder and ASD, many comorbid symptoms may co-exist and include cognitive and intellectual disabilities, language deficits, motor abnormalities, attentional difficulties, hyperactivity,

1 Diagnostic and Statistical Manual of Mental Disorders (DSM): DSM-IV

affective difficulties (e.g., anxiety and depression), interfering repetitive activity, irritability, aggression, self injurious behavior, and sleep disruptions.

In 2006 the Center for Disease Control (CDC) estimated that an average of 1 in 110 children in the U.S. had an ASD[2]. The risk is 3 to 4 times higher in males than females. The number of children with ASDs has risen dramatically over the past decade and has resulted in a public health concern. The previously reported prevalence was about 4 to 5 per 10,000 children. The reasons for this increase are not well understood. Some of the reported increases are attributed to new administrative classifications in special education settings and the reclassification of children from a different diagnostic category to autism, and the early detection of at risk children, prior to age of 3 years, to allow for early intervention services. However, environmental factors and gene–environment interactions, including epigenetic factors, are also thought to play a role.

Current Drug Treatments for Autism (Autistic Disorder):

There are currently no medications specifically approved in the US for the treatment of any of the core domains of autism. Risperdal® (risperidone) and Abilify® (aripiprazole) are indicated for the treatment of irritability associated with autistic disorder in children and adolescents aged 5 to17 years, including symptoms of aggression toward others, deliberate self-injuriousness, temper tantrums, and quickly changing moods.

A number of medications are prescribed for treatment of specific ASD-related symptoms, such as anxiety, attention difficulties, depression, obsessive-compulsive disorder, sleep difficulties and severe maladaptive behavioral problems. These include stimulants, serotonin reuptake inhibitors, atypical antipsychotics, α-2 agonists, anticonvulsants, omega 3 fatty acids and melatonin. Families also often use various complementary and alternative medical treatments[3]. Many of these treatments are un-supported by scientific studies. Alernative treatments include nutritional supplements (Vitamin B6, magnesium ion, dimethyl glycine, and cod-liver oil), anti-infectives (antibiotics, antifungals, and antivirals), immunoglobulins, secretin, chelation medications, gastrointestinal medication, elimination or special diets (gluten or casein free), and hyperbaric oxygen administration.

Current Off-Label Use of Memantine in the Pediatric Population:

A Drug Utilization Review[4] conducted as part of the background for this Written Request found that pediatric use of memantine in Autistic Disorder, from August 2005 though July 2011, was 0.8% or 8,000 (95% CI, 0 – 21,000). “Down’s Syndrome” (ICD-9 code 758.0) was the top diagnosis code associated with the use of memantine in the pediatric population aged 0-17 years with approximately 68% or 43,000 (95% CI, 12,000 – 74,000) drug use mentions. Patients aged 6-12 years accounted for the majority of pediatric prescriptions and males accounted for a greater proportion of use in the

2Autism and developmental disabilities Monitoring Network Surveillance Year 2006 Principal Investigators; Centers for Disease Control and Prevention (CDC). Prevalence of autism spectrum disorders: autism and developmental disabilities monitoring network, United States, 2006. MMWR Surveill Summ 2009; 58:1–20.

3 Levy SE et. al. Autism, Lancet. 2009 Nov 7; 374 (9701): 1627-38.

4 Misty K, Chai G, Governale L. Namenda® (memantine hydrochloride) Drug Utilization for PeRC Meeting relating to NDA 21-487, NDA 21-627, NDA 22-525; OSE RCM No. 2011-3475; November 02, 2011

pediatric population. The most commonly used strength among pediatric patients was 10 mg. The most frequently prescribed medication for the diagnosis of Autistic Disorder in the pediatric population ages 0-17 years was risperidone, accounting for 33% or 347,000 (95% CI, 259,000 – 435,000) of drug use mentions.

Pediatric Post-Marketing Adverse Events Associated with the Use of Memantine

As part of the background for this Written Request, the Division of Pharmacovigilance (DPV) searched and assessed the FDA Adverse Event Reporting System (AERS) for all adverse events in pediatric patients associated with the use of memantine[5] for the period October 16, 2003 – September 22, 2011. In the 11 cases, they identified, they did not identify any new safety concerns in the pediatric population associated with the use of memantine.

Juvenile Animal Study

Based upon animal studies, neurotoxicity from drugs that block NMDA receptor channels, like memantine, is a concern. Studies in rodents and non-human primates have indicated that other drugs in this class cause apoptotic lesions in brains of young animals; and studies in rodents have indicated that memantine and other drugs in this class cause vacuolation and neurodegeneration in brains of mature rodents. We acknowledge that you have already conducted a toxicology study in juvenile rats (starting at post-natal day 14) to support administration to children 6 years of age and older. Based upon neurodegeneration observed in specific brain areas of post-natal day 14-17 rats, the systemic exposure in children (greater than 6 years of age) has been limited to one tenth that at the no adverse effect level (NOAEL) in juvenile rats (i.e., AUC limited to not more than 2100 ng.hr/ml),

To obtain needed pediatric information on memantine, 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 the clinical efficacy and safety studies described below.

Specific Study Requirements for a Development Program in Children Autistic Disorder

Overall Objectives/Rationale

The overall goal of the development program is to establish the safety and efficacy of memantine in the treatment of the core symptoms of autism or autistic spectrum disorder.

The required studies include:

- Nonclinical Toxicology Study
- Pharmacokinetic Study
- Pediatric (ages 6-12 years) Efficacy and Safety Studies
- Pediatric (ages 6-12 years) Safety Studies

5 Diak I-L, Scarazzini LJ. Adverse Event Reports for Pediatric Use of Memantine; IND 73075; OSE RCM No. 2011-3475; October 05, 2011

Study Design

Nonclinical Toxicology Study

The data from your study of memantine in juvenile rats (dosed from postnatal day 14) that you have already submitted, including special evaluation of neurohistopathological changes, are adequate to support initiation of clinical trials in children 6 years of age and older. Since we have deemed these data to be adequate, this study is not a part of this Written Request.

However, to further investigate the neurotoxicity (apoptosis and necrosis/degeneration) of memantine in children and to obtain adequate data on reproductive toxicity, you must conduct a study in juvenile rats, with dosing starting at post-natal day 7. In the main study, rats must be treated to maturity (i.e., PND 70) and, in addition to the usual toxicological parameters, this study must evaluate the effects of memantine on growth, reproductive development, and neurological and neurobehavioral development. Reproductive effects need to be evaluated following cessation of treatment; there should be a washout period of appropriate duration (depending on the half-life) between cessation of treatment and evaluation. In assessing neurobehavioral development, the effects should be evaluated during treatment and after an appropriate washout period following the cessation of treatment (to evaluate potential long-term effects). To avoid the confounding effect of repeated neurobehavioral testing, separate groups of animals should be used at the two assessment times. However, to avoid unnecessary use of animals, the same group of animals may be used to evaluate neurobehavioral effects during treatment and the effects on reproductive parameters. The neurobehavioral tests must assess sensory function, motor function, and learning and memory. The neuropathological evaluation must include examination of all major brain regions, with particular attention to alterations indicative of developmental insult. In addition, because memantine is an NMDA receptor channel blocker, a separate set of rats must be evaluated for neurohistopathological changes, including apoptosis and necrosis/neurodegeneration, after single doses, using appropriate neurohistopathological staining tools. Systemic exposures (C_{max} and AUC) must be assessed after single dosing and after repeated dosing, for comparison to exposures in children. You must submit a detailed protocol for this study to the Division for our comments before the initiation of this study.

You must submit a plan for assessing the neurotoxicity of memantine in non-human primates, with the design and endpoints based upon the results of the findings in the studies in rats. Completion of such a study and submission of its results is not, however, a part of this Written Request.

Pediatric Pharmacokinetic Study

Ideally, pediatric PK data for memantine would be used to inform your dosing strategy in your pediatric efficacy and safety studies. We acknowledge that you have submitted the data for your pediatric PK study in children and adolescents ages 6 to 17 years. We consider these data adequate to fulfill this requirement, and therefore, further conducting such a study is not a part of this Written Request.

Pediatric Efficacy and Safety Studies

As part of this Written Request, you must conduct two (2) randomized, double-blind, placebo-controlled trials. The primary goal of these studies would be to evaluate the efficacy and safety of memantine in the treatment of core features of autism or autistic spectrum disorder. Complete information about the reasons for subjects leaving each trial must be collected and provided. You are required to employ a weight based dosing strategy in these trials. In order to assess the potential dose-response relationship for effectiveness and tolerability as well as to inform labeling recommendations on dosing, at least one of the two studies has to be a weight based fixed dose study and at least two different doses need to be studied.

One of the two (2) efficacy studies must be a randomized, double-blind, parallel group, 12-week study utilizing a weight based dose with an AUC exposure limit of 2100 ng.h/ml. The other efficacy study must be a double-blind, placebo-controlled, randomized withdrawal study in patients who have received a minimum of 12 weeks exposure to the drug. Patients who are responders to the drug treatment and have been stabilized with the drug, i.e., meet responder criteria for 2 consecutive visits, would be eligible to be randomized to memantine treatment or placebo. Patients would be observed for relapse during the double-blind phase. A "responder" must be defined as patients who show a 10 point improvement on the Social Responsiveness Scale (SRS) total score relative to their pre-treatment scores. The criteria for "relapse" must be defined as worsening by 10 points on the SRS total score relative to the score obtained immediately before randomization.

If the results from the additional juvenile rat study support a clinical study in patients younger than 6 years old, you will need to commit to conducting additional efficacy and safety studies in younger and older pediatric patients, i.e., a safety study in children ages 3 to 5, and an efficacy study in adolescents ages 13 to 17 years old. The study protocols would then need to be submitted for the Agency's concurrence to meet the requirement of this written request. Completion of such studies and submission of their results would not, however, be considered a part of this Written Request.

Pediatric Safety Study

Also as part of this Written Request, you must collect safety data in the controlled efficacy trials. You must collect longer-term safety data for a minimum duration of 6 months exposure to the drug. The longer-term safety data could derive from open-label studies, e.g., a longer-term open extension of the short-term controlled efficacy trial population, or from a separate longer-term open safety study, or from the randomized withdrawal study. The long-term safety data must be at the doses identified as effective in the controlled studies.

Patients to Be Studied

Age group in which study(ies) will be performed

Children ages 6 to 12 years must be included in the sample. The gender distribution of participants in this study must reflect the distribution in those affected with this condition.

Number of Patients to Be Studied

Pediatric Efficacy and Safety Studies

The studies must have sufficient numbers of subjects to provide at least 85% statistical power to detect a clinically meaningful treatment benefit on an acceptable primary endpoint. The Social Responsiveness Scale (SRS) total score would be acceptable as the primary efficacy measure. If you choose to use change from baseline in SRS total score as the primary endpoint for your short-term, randomized, double-blind, parallel group study, the trial must be powered to show a ten-unit difference between drug and placebo. For your randomized withdrawal study, your statistical analysis plan must explain how you intend to demonstrate and ensure 85% statistical power. To ensure adequate statistical power in these studies, you must conduct interim analyses late in the trials for a sample size increase if necessary (see Statistical Information).

Pediatric Longer-Term Safety Study

A sufficient number of pediatric subjects to adequately characterize the safety of the study drug over a longer period of time at clinically relevant doses identified as effective in an adequately designed trial reflecting the proposed use of the drug. At least 100 subjects with autism or autism spectrum disorder who have been exposed to memantine for at least 6 months is the minimum requirement for long-term safety.

Representation of Ethnic and Racial Minorities

The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

Entry Criteria

The protocol must include a valid and reliable diagnostic method for recruiting and enrolling children ages 6 to 12 years meeting DSM-IV criteria for Autistic Disorder or Autistic Spectrum Disorder (i.e., Asperger's Syndrome, and Pervasive Developmental Disorder-Not Otherwise Specified).

Study endpoints

Pediatric Efficacy and Safety Studies

Efficacy Endpoint

Scales specific to severity of autistic spectrum disorder core symptoms and sensitive to the effects of drug treatment of autistic spectrum disorder in the target population must be used. The assessments have to be well validated in the target populations. The Social Responsiveness Scale total score measuring reciprocal social behavior associated with autistic spectrum disorder must be used as a primary efficacy measure.

Safety Endpoints

Routine safety assessments must be collected at baseline and appropriate follow-up times, e.g., vital signs (pulse rate and blood pressure), weight, height, clinical laboratory measures (chemistry, including liver function tests and bilirubin, hematology, and urinalysis), ECGs, and monitoring for adverse events.

Given concerns regarding the neuronal injury observed in the rat juvenile study, appropriate cognitive testing, such as the Kaufman Brief Intelligence Test (KBIT2), must be evaluated at baseline and at the end of the study in your randomized withdrawal trial.

Pediatric Safety Study

Similar safety assessments as described above in *Pediatric Efficacy and Safety Studies* must be performed at baseline and appropriate follow up times.

Statistical Information, Including Power of Study(ies) and Statistical Assessments

Pediatric Efficacy Studies

These trials must each have a detailed statistical plan. The trials must be designed with at least 85% statistical power to detect a clinically meaningful treatment effect at conventional levels (alpha=0.05, 2-tailed) of statistical significance.

For your randomized withdrawal trial, a preliminary statistical analysis plan must be submitted for comment prior to initiating this trial, and you must obtain agreement on the final statistical plan prior to 45% enrollment. Unless the initial sample size is convincingly large, the statistical analysis plan must include a plan for an interim analysis, to ensure adequate power for this study.

For the randomized, double-blind, parallel group, 12-week study, a clinically meaningful treatment benefit must be defined as a 10 unit difference between drug and placebo in change from baseline to endpoint on the SRS total score. You must conduct a blinded interim analysis to estimate the variance for potential sample size increase.

Any interim analyses for the studies must be pre-specified and you must follow the pre-specified rules to adjust the sample size to achieve the specified target power. Such an interim analysis must be performed by an independent third party when the studies are close to finishing (for example, at >90% of initially planned enrollment).

Pediatric Efficacy and Safety Studies

A descriptive analysis of the safety data must be provided.

GENERAL REQUIREMENTS AND COMMENTS

Drug information:

- *dosage form: 3 mg and 6 mg capsules*
- *route of administration: oral*

- *regimen: once daily*

Use an age-appropriate formulation in the study(ies) 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:

Memantine has potentially serious neuro-toxicity based on pre-clinical data. NMDA receptor blockade may result in potential cell death/loss in the mature and developing brains. Large amounts of memantine given to rats caused damage to different areas of the brain. The amount of the drug given to the rats was higher than proposed doses in these studies. Appropriate cognitive assessment is required at baseline and at the end of the study in your randomized withdrawal trial.

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 study(ies):

You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that memantine 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 study(ies). 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 study(ies).

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 study(ies) 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 http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.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/RegulatoryInformation/Guidances/ucm126959.htm

Timeframe for submitting reports of the study(ies):

Reports of the above studies must be submitted to the Agency on or before December 7, 2014. 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 study(ies). 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 study(ies), 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 study(ies) 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 study(ies) 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.

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/s/

ELLIS F UNGER
05/29/2013