DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204370

WRITTEN REQUEST – AMENDMENT 2

Allergan Sales, LLC
Attention: Melina Cioffi, PharmD
Director, Regulatory Affairs
5 Giralda Farms
Madison, NJ 07940

Dear Dr. Cioffi:

Please refer to your correspondence dated February 16, 2018, requesting changes to FDA's February 3, 2017 Written Request for pediatric studies for Vraylar (cariprazine).

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 February 3, 2017, and as amended on November 30, 2017, remain the same. (Text added is underlined. Text deleted is strikethrough.)

Nonclinical study(ies):

Based on review of the available non-clinical toxicology, the following study/studies must be conducted prior to the start of dosing the corresponding age cohorts in ~~prior to the start of~~ the clinical study/studies described in this written request.

Clinical studies:
Study 5: Pediatric long-term safety study

- ☐ The pharmacokinetic data for doses studied in patients ages 13-17 years must be submitted and reviewed by the Agency prior to administering the corresponding dose ~~initiation of the PK study~~ in patients ages 5-12 years in the PK study.

- ☐ The sponsor may decide to evaluate long-term safety as open-label extensions to the acute efficacy studies (Studies 2, 3, and 4) or as one or two dedicated long-term safety studies. In such cases, the sponsor will provide a combined total of at least 100 patients with 6 months of cariprazine exposure from the combined long-term studies. ~~same amount of data will be generated as would be expected in a separate long-term safety study.~~

Safety endpoints:
~~You must conduct complete ophthalmology examinations at baseline, after randomization, and at four to six month intervals throughout the studies. These studies should include ocular examinations, including, at a minimum, visual acuity testing, fundus photography, and macular ocular coherence tomography (OCT) testing. visual acuity, color vision testing, and slit-lamp assessment. Provide the initial and subsequent detailed ophthalmology records, including copies of any images made.~~

You must conduct complete ophthalmology examinations (i.e., visual acuity test, fundus photography and macular ocular coherence tomography (OCT)) at baseline (after randomization), at the end of double blind treatment, and at four to six month intervals for the duration of each subject's study enrollment. Provide the initial and subsequent detailed ophthalmology records, including copies of any images made.

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 February 3, 2017, as amended by this letter and by previous amendment dated November 30, 2017, must be submitted to the Agency on or before June 30, 2025, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an 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 accordance with section 505A(k)(1) of the Act, 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:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
- the action taken (i.e., approval, complete response); or
- 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, 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 Danbi Lee, Regulatory Project Manager, at danbi.lee@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Ellis F. Unger, MD
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Complete Copy of Written Request as Amended

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204370

WRITTEN REQUEST

Forest Research Institute, Inc., an affiliate of Forest Laboratories, LLC
Attention: Melina Cioffi, PharmD
Director, Regulatory Affairs
Harborside Financial Center
Plaza V, Suite 1900
Jersey City, NJ 07311

Dear Dr. Cioffi:

Reference is made to your September 27, 2016, Proposed Pediatric Study Request for Vraylar (cariprazine) Capsules, 1.5 mg, 3 mg, 4.5 mg and 6 mg.

BACKGROUND:

These studies investigate the potential use of cariprazine in the treatment of pediatric patients ages 13 to 17 with schizophrenia and ages 10 to 17 with acute manic or mixed episodes associated with bipolar I disorder, and ages 5 to 17 with autism spectrum disorder.

Schizophrenia
Schizophrenia is a chronic and debilitating illness that has an estimated lifetime adult prevalence of 0.5 to 1%. According to the DSM IV, the diagnostic criteria for schizophrenia are the same for the pediatric and adult populations, but the symptomatology and prevalence of schizophrenia in these two populations have been recognized to be somewhat different. Within the pediatric age group, a diagnosis of schizophrenia is most commonly made in adolescents, and the symptoms in this age group are generally similar to those in adults (APA Practice Parameters, 1997). Schizophrenia has also been described in children, but it is thought to be uncommon (AACAP Practice Parameters, 2001). Although there are not adequate epidemiological data, one author suggests that 0.1 to 1% of schizophrenic psychoses will present prior to age 10 (Remschmidt, 1996). In addition, the symptoms in childhood schizophrenia differ from those typically seen in adult schizophrenia and the diagnosis is more difficult to establish in this younger population (Volkmar, 1996).

Given the finding that childhood onset schizophrenia may present with symptoms quite different from those of adult onset schizophrenia, it would be important to systematically study the efficacy of treatment within this pediatric population, ages 12 and under. The very low incidence of schizophrenia diagnosed prior to the age 13, including neonates, makes it unlikely that it would be possible to conduct a sufficiently large study of this age group within a reasonable time.

Under current regulations [21 CFR 201.57(c)(9)(iv) in the 2009 CFR], a new claim in an adolescent 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 schizophrenia was essentially the same disease in adults and adolescent patients. Under FDAMA (1997), a claim might be based on a single study in adolescent patients along with confirmatory evidence from another source, perhaps adult data for that disorder, an approach considered in the 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 adolescent and adult populations to make data from the adult efficacy studies pertinent to adolescent patients. We believe that a sufficiently strong case has been made for continuity between adult and adolescent schizophrenia to permit an adolescent claim for a drug already approved in adults to be supported by a single, independent, adequate and well-controlled clinical trial in adolescent schizophrenia. In addition, an adolescent schizophrenia program would need to include pharmacokinetic information and safety information in adolescents (13-17) with schizophrenia.

Bipolar I 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 10 to 17 year-old population is thought to be relatively common and phenomenologically similar to bipolar disorder seen in adults. Thus, the study of bipolar disorder in 10 to 17 year-olds should be feasible and should yield useful information.

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 bipolar disorder was essentially the same disease in adults and pediatric patients. 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 pediatric and adult populations to make data from the adult efficacy studies pertinent to pediatric patients. We believe that a sufficiently strong case has been made for continuity between adult and pediatric bipolar disorder to permit a pediatric claim for a drug already approved in adults to be supported by a single, independent, adequate and well-controlled clinical trial in pediatric bipolar disorder. In addition, a pediatric bipolar program would need to include pharmacokinetic information and safety information in pediatric patients in the 10-17 age range with bipolar disorder.

Autism Spectrum Disorder

Autism Spectrum Disorder (ASD) is a neuro-developmental disorder characterized by impairments in social interactions, communication, and restricted interests and stereotyped behaviors. In 2014, the CDC estimated that an average of 1 in 68 children in the United States has an ASD. The risk is 3 to 4 times higher in males than females. ASD is characterized by persistent deficits in social communication and social interaction, and restricted, repetitive patterns of behavior, interests or activities. These symptoms are present from early childhood, often recognized in children age 2 years or younger.

There are currently no medications specifically approved in the US for the treatment of the core features of ASD. Risperidone and aripiprazole are indicated for the treatment of irritability associated with autistic disorder in patients 5 to 17 years of age (6 to 17 years for aripiprazole, 5-16 years for risperidone); this includes symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods. It is likely that other antipsychotics, including cariprazine, will be used off-label for the treatment of irritability in children and adolescents with autistic disorder. Therefore, it is important to evaluate the efficacy and safety of other atypical antipsychotics, including cariprazine, in this patient population.

To obtain needed pediatric information on cariprazine, 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 studies described below.

- *Nonclinical study(ies)*:

Based on review of the available non-clinical toxicology, the following study/studies must be conducted prior to the start of dosing the corresponding age cohorts in the clinical study/studies described in this written request.

Study 1: A 9-week toxicity study in the juvenile rat starting at the appropriate age that corresponds to children age of 5 years. This study must be completed prior to initiation of pediatric clinical studies in children < 13 years of age.

Study 2: A 26-week toxicity study in the juvenile dog starting at the appropriate age that corresponds to children age of 5 years. This study must be completed prior to initiation of pediatric clinical studies in children < 13 years of age.

- *Clinical studies:*

Study 1: A 12-week pediatric pharmacokinetic study in two populations: 1) ages 13-17 years, and 2) ages 5-12 years.

Study 2: Adequate and well-controlled pediatric efficacy and safety study in patients with schizophrenia

Study 3: Adequate and well-controlled pediatric efficacy and safety study in patients with acute manic or mixed features associated with bipolar I disorder

Study 4: Adequate and well-controlled pediatric efficacy and safety study in patients with irritability associated with ASD

Study 5: Pediatric long-term safety study

- ☐ The nonclinical studies in support of dosing patients ages 5-12 years must be completed and draft results reported to the Agency prior to the initiation of clinical studies in those patients. Final reports will be submitted to the Agency once available.

☐ The pharmacokinetic data for doses studied in patients ages 13-17 years must be submitted and reviewed by the Agency prior to administering the corresponding dose in patients ages 5-12 years in the PK study.

☐ The pharmacokinetic study (or studies) in support of dosing patients ages 5-12 years must be completed and topline results reported to the Agency prior to the initiation of the efficacy trial(s) in those patients to inform dosing.

☐ The sponsor may decide to evaluate long-term safety as open-label extensions to the acute efficacy studies (Studies 2, 3, and 4) or as one or two dedicated long-term safety studies. In such cases, the sponsor will provide a combined total of at least 100 patients with 6 months of cariprazine exposure from the combined long-term studies.

☐ For each study, the sponsor must submit a protocol for review and approval by the Agency prior to the initiation of the study.

- *Objective of each study:*
  - *Study 1:* To evaluate multiple-dose pharmacokinetics, safety, and tolerability of cariprazine and its major active metabolites in pediatric patients 5 to 17 years of age.
  - *Study 2:* To evaluate the efficacy, safety, and tolerability of cariprazine in pediatric patients ages 13 to 17 with schizophrenia.
  - *Study 3:* To evaluate the efficacy, safety, and tolerability of cariprazine in pediatric patients ages 10 to 17 with acute manic or mixed features associated with bipolar I disorder.
  - *Study 4:* To evaluate the efficacy and safety of cariprazine in the treatment of irritability associated with autism spectrum disorder in pediatric patients ages 5 to 17 years.
  - *Study 5:* To evaluate the long-term safety of cariprazine in pediatric patients with schizophrenia, bipolar I disorder, or ASD.

- *Patients to be Studied:*

  - *Age group in which study(ies) will be performed*:

    Study 1: Patients with schizophrenia ages 13 to 17 years, with bipolar I disorder ages 10 to 17 years, or patients with ASD 5 to 17 years

    Study 2: Patients with schizophrenia ages 13 to 17 years

    Study 3: Patients with bipolar I disorder ages 10 to 17 years

    Study 4: Patients with ASD ages 5 to 17 years

    Study 5: Patients with schizophrenia ages 13 to 17 years, with bipolar I disorder ages 10 to 17 years, or with ASD ages 5 to 17 years

  - *Number of patients to be studied:*

    Study 1

    ☐ A sufficient number of patients to adequately characterize the appropriate dose range, tolerability, and pharmacokinetics of the study drug and its major active

metabolite(s) in the relevantage group must be studied.

- The gender distribution of participants in this study must reflect the distribution of those affected with this condition.
- The study must be prospectively powered to target a 95% confidence interval (CI) within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution for parent drug in the entire age range, or utilize a method justified by the Sponsor and agreed upon with the Agency.

Studies 2, 3, and 4

- Each trial must have a sufficient number of patients to provide 85% statistical power to show a clinically meaningful difference between drug and placebo. For the purpose of satisfying the Written Request, the treatment effect might, for example, be defined as a 5-unit difference between drug and placebo in change from baseline on the PANSS total score for the schizophrenia study, and a 4.5 unit difference in change from baseline to endpoint on the YMRS for the bipolar I disorder study. The irritability subscale of the Aberrant Behavior Checklist (ABC) would be acceptable as the primary efficacy measure for the required study for irritability associated with autism. If you choose to use change from baseline in the irritability subscale of the ABC as the primary endpoint, the study should be powered to show a 6-unit difference between drug and placebo. You must conduct an interim analysis to estimate variance late in the trial, and increase the sample size if necessary to ensure that the trial has adequate power (see Statistical Information).

Study 5

- This study must include a sufficient number of pediatric patients to adequately characterize the safety of the study drug at or above the dose or doses identified as effective in an adequately designed trial or, if this trial fails to detect a drug effect, at doses equivalent to the adult exposure of the drug. A combined total of at least 100 patients with schizophrenia, autism spectrum disorder, and bipolar disorder together and exposed to drug for at least 6 months, would be a 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.

- *Study endpoints:*

  - ☐ *Pharmacokinetic Endpoints:*
    The Sponsor must measure and collect data to develop adequate estimates of the pharmacokinetic profile, including important pharmacokinetic parameters for the parent compound and major active metabolites, i.e., AUC, half-life, C_{max}, T_{max}, and apparent oral clearance (this parameter for parent only). These estimates of pharmacokinetic parameters must be obtained using sufficient sampling.

  - ☐ *Efficacy Endpoints;*
    A scale specific to schizophrenia and sensitive to the effects of drug treatment of

schizophrenia (for Study 2), bipolar I disorder (for Study 3), or irritability associated with ASD (for Study 4) in the target population must be used. The choice of the primary assessment instrument and the primary outcome will need to be justified and approved by the Agency. Specifically, if you choose scales and outcomes used in adult trials, you will need to justify that these measures are appropriate for use in the pediatric population. Alternatively, you may perform preliminary trials to identify sensitive rating scales in this population. It is essential to identify a primary outcome for the controlled efficacy trial; ordinarily this would be change from baseline to endpoint on whatever symptom rating scale you have chosen for your trial.

☐ *Safety Endpoints:*

☐ Safety outcomes must include routine safety assessments collected at baseline and appropriate follow-up times, e.g., vital signs (pulse rate and blood pressure), weight, height, as measured by stadiometer, clinical laboratory measures (chemistry, including liver function tests and bilirubin; hematology; serum lipids; and urinalysis), ECG's, and monitoring for adverse events (including extrapyramidal symptoms and dyskinesias). Given recent concerns regarding psychiatric adverse events with psychiatric medication use, particularly in children, you must provide an assessment of psychiatric adverse events (i.e., worsening of psychosis, depressed mood, suicidal and homicidal ideation) as part of this written request.

☐ The following adverse events must be actively monitored:

- You must adequately assess antipsychotic class safety concerns including hyperglycemia, leucopenia/neutropenia/agranulocytosis, orthostatic hypotension/bradycardia/syncope, QTc prolongation, akathisia and other extrapyramidal symptoms, weight gain, and somnolence.
- 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 would need to be included in every clinical protocol, at every planned visit, and in every phase of development.
- You must conduct complete ophthalmology examinations (i.e., visual acuity test, fundus photography and macular ocular coherence tomography (OCT)) at baseline (after randomization), at the end of double blind treatment, and at four to six month intervals for the duration of each subject's study enrollment. Provide the initial and subsequent detailed ophthalmology records, including copies of any images made.

All adverse events must be monitored until symptom resolution or until the condition stabilizes.

☐ A Data Monitoring Committee (DMC) must be included because findings of futility at an interim analysis may ethically require termination of the study before its planned completion. See Guidance: Establishment and Operation of Clinical Trial Data Monitoring Committees http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126578.pdf

- *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.

- *Drug information:*

  - *dosage form:* capsule
  - *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 prepared 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 preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation 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.

- *Statistical information, including power of study(ies) and statistical assessments:* Clinical Studies 2, 3 and 4 must all have detailed statistical analysis plans (SAPs). The preliminary SAPs must be submitted for comment and you must obtain agreement on the final plans prior to initiation of the studies. 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 on the treatment effect (postulated magnitude of treatment effect along with its standard deviation) used for sample size calculation prior to initiating the studies.

  To ensure your 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. Such interim analyses must be performed when the studies are close to completion (for example, when >75% of initially randomized patients have completed/ discontinued). You may estimate the variability based on a blinded and pooled analysis of all groups. If you want to perform an interim efficacy assessment at this time or at some other point in time, you must propose an appropriate alpha adjustment method.

  With respect to the primary efficacy analysis, the protocols will describe the estimand of primary interest. If the estimand of interest is the treatment effect in all patients randomized regardless of adherence, you should include provisions to limit missing data through study design and education of investigators and patients, and pre-specify analysis methods to account for missing data for the primary and key secondary efficacy analyses. If you believe the treatment effect in all patients randomized regardless of adherence is not the most clinically important estimand, the protocol should specify which estimand is of most clinical importance and why. Statistical methods to quantify this estimand should be specified in the protocol.

- *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 cariprazine 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/Cder/guidance/7087rev.htm.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before June 30, 2025.

  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, CDER, FDA, Document Control Room, Metro Park North VII, 7620 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, contact Danbi Lee, Regulatory Project Manager, at danbi.lee@fa.hhs.gov.

Sincerely,

{See appended electronic signature page}

Ellis F. Unger, MD
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
11/30/2017

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/s/

ELLIS F UNGER
06/15/2018