DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022181

WRITTEN REQUEST

BioMarin Pharmaceutical, Inc.
Attention: Ben Dewees
Associate Director, Regulatory Affairs
105 Digital Drive
Novato, CA 94949

Dear Mr. Dewees:

Reference is made to your May 5, 2010, Proposed Pediatric Study Request (PPSR) for Kuvan (sapropterin dihydrochloride).

BACKGROUND:

These studies investigate the potential use of sapropterin dihydrochloride in the treatment of pediatric patients with tetrahydrobiopterin- (BH4) responsive phenylketonuria (PKU), ages 0 months (birth) through six years of age, inclusive. Effectiveness will be extrapolated from studies in older pediatric patients using a proven surrogate endpoint, since the pathophysiology of PKU is the same in all age groups.

PKU is a rare, autosomal recessive disorder that occurs as a result of reduced or absent activity of the enzyme phenylalanine hydroxylase. PKU affects approximately 1 in 10,000 to 1 in 15,000 people in the United States. Affected infants are normal at birth. However, untreated patients develop elevated blood phenylalanine (Phe) levels and subsequent adverse neurological symptoms including severe mental retardation, hyperactivity and seizures. PKU is usually diagnosed in the newborn period because newborn screening for PKU is conducted in all states. Adverse neurological outcomes are ameliorated or prevented by decreasing blood phenylalanine with dietary phenylalanine restriction. However, it is not possible to reverse established neurocognitive decline. Prior to the approval of sapropterin dihydrochloride, PKU was managed exclusively with a low-phenylalanine diet. Sapropterin dihydrochloride is a synthetic form of tetrahydrobiopterin (BH4) and was approved in 2007 to reduce blood Phe levels in patients with BH4-responsive PKU. Early intervention with sapropterin dihydrochloride may improve clinical outcomes by lowering blood Phe levels in those patients with BH4-responsive PKU.

Approval of sapropterin dihydrochloride was based on 4 clinical studies evaluating the efficacy and safety of the drug in PKU patients ages 4 years and older. However, no clinical trials have been performed to evaluate the efficacy and safety in PKU patients birth to 4 years of age. The product is intended to be used in pediatric populations as early as the newborn period to avoid serious neurocognitive sequelae. Therefore, clinical trials should be conducted in this patient population. Additionally, only one clinical study submitted in the original NDA included

patients 4-8 years of age (n=90). The mean age of patients enrolled in this study (PKU-006) was 7.3 (± 2.5) years. Therefore, additional data in patients 4-6 years of age are also necessary.

It should be noted that this Pediatric Written Request (WR) is the second WR issued for Kuvan. The original WR was issued on January 14, 2008. A Type C meeting was held on September 15, 2008 to discuss your requested revisions to the WR. Based on agreements obtained at this meeting, an amendment to the WR was submitted on February 4, 2009. However, the amendments to the WR were not reviewed and approved prior to the expiration of the original WR on May 31, 2009. Therefore, the FDA review division communicated to you via email on January 25, 2010 that a new PPSR should be submitted so that a new WR could be issued. This communication also included specific recommendations for the PPSR based on agreements reached during the September 2008 Type C meeting. A new PPSR was submitted on May 5, 2010. However, studies were initiated under the amended WR based on the agreements reached during the Type C meeting, and in fact, the studies are near completion at this time. The current WR is being issued to include agreements made during the Type C meeting held on September 15, 2008 and to replace the WR that expired on May 31, 2009.

To obtain needed pediatric information on sapropterin dihydrochloride, 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 studies*:**

Nonclinical toxicology studies were conducted in rats (104 weeks duration) and mice (78 weeks duration) to support the original NDA for sapropterin dihydrochloride. In both groups, sapropterin doses of 25, 80, and 250 mg/kg/day were used. According to current labeling, sapropterin at oral doses up to 400 mg/kg/day (about 3 times the maximum recommended human dose, based on body surface area) was found to have no effect on fertility and reproductive function of male and female rats. Based on review of the available nonclinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.

Clinical studies:

Study 1: PK-PD and Tolerability Study

A 4-Week Pharmacokinetic/Pharmacodynamic (PK-PD) and tolerability study in pediatric patients birth to 6 years with PKU. All patients must have their diet controlled for Phe intake at entry and throughout the study. Patients will receive sapropterin dihydrochloride at 20 mg/kg/day. Response to treatment will be defined as a $\geq$ 30% decrease from baseline blood Phe levels (measured at point of entry into the PD study) at the end of the PD study (e.g., 4 weeks of treatment). Patients who are tetrahydrobiopterin- (BH4) responders will be enrolled in the 6-month, open-label efficacy and safety study (Study 2). Patients who are unable to achieve the target exposures due to tolerability issues will need to receive a total of 6 months of exposure at the last tolerated dose that provided an acceptable response to treatment.

Study 2: Safety and Efficacy Study
A 6-month, open-label, uncontrolled, efficacy and safety study of sapropterin dihydrochloride in pediatric patients birth to 6 years with BH4-responsive PKU. All patients must have their diet controlled for Phe intake at entry and throughout the study. Patients who completed the 4 week PK/PD study (Study 1) and were found to be responders will be enrolled in this study. Patients (BH4 responders) will receive sapropterin dihydrochloride for an additional 5 months on Study 2 for a total of 6 months at doses expected to achieve exposures of sapropterin observed in older pediatric patients. Patients who are unable to achieve the target exposures due to tolerability issues will need to receive a total of 6 months of exposure at the last tolerated dose that provided acceptable response to treatment. Effectiveness will be extrapolated from studies in older pediatric patients using a proven surrogate endpoint since the pathophysiology of PKU is similar in all pediatric age groups.

A minimum of 60 BH4-responsive patients with PKU (responders) from Study 1 will be enrolled in Study 2. Patients will receive a total of six months of treatment with sapropterin dihydrochloride. The number of patients enrolled into Study 1 should be estimated based on the projected number of responders (defined as patients who demonstrate a ≥ 30% decrease in blood Phe from baseline at the end of Study 1), and on the projected number of drop-outs over the course of Study 1 and Study 2.

Objective of each study:

Study 1: PK-PD and Tolerability Study
To evaluate the population pharmacokinetics of sapropterin dihydrochloride administration for up to 4 weeks of treatment in pediatric patients ages 0 months to 6 years.

To evaluate safety and identify those pediatric patients ages 0 months to six years who will respond to sapropterin dihydrochloride (as defined as a ≥ 30% decrease from baseline blood Phe Levels) after 4 weeks of treatment.

Study 2: Safety and Efficacy Study
To evaluate the safety and tolerability of sapropterin dihydrochloride administration for a total of six months of treatment to pediatric patients with PKU, ages 0 months to six years. The efficacy outcome variable is the change in blood Phe level from baseline (no treatment) at the end of six months of treatment in the subgroup of patients who respond to treatment with sapropterin dihydrochloride (BH4 responders) in Study 1. Safety assessments must include, at minimum, physical examinations (to include, at a minimum, height, weight, and head circumference), medical history, and safety laboratory collections (including, at minimum, chemistry panel, complete blood count, and urinalysis) at baseline and at intervals during treatment, and the collection of Adverse Events during treatment.

Growth and neurocognitive development must be assessed periodically as age-appropriate. Standardized and replicated measurements of head circumference (less than 3 years of age), weight and length/height must be obtained. Neurocognitive development must be assessed using well validated and age-appropriate measures, including the Bayley III.

Indication to be studied:

Treatment to reduce blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to BH4-responsive PKU.

Patients to be studied:

Study 1: PK-PD and Tolerability Study
Pediatric patients ages 0 months to 6 years who have PKU.

Study 2: Safety and Efficacy Study
Pediatric patients ages 0 months to 6 years who have completed PK-PD Study (Study 1) and have BH4-responsive PKU.
Age group in which studies will be performed:

Birth to <1 year
1 year to 2 years
2 years to 4 years
4 years to 6 years

Number of patients to be studied:

Study 1: PK-PD and Tolerability Study
The number of patients should be estimated based on the projected number of responders, and on the projected number of drop-outs over the course of the study to ensure adequate enrollment for the Safety and Efficacy Study (Study 2). BH4-responsive patients will be defined as patients who demonstrate a ≥ 30% decrease in blood Phe from baseline at the end of Study 1 (while on a PKU-controlled diet).

For an adequate population pharmacokinetic analysis, the study must be prospectively powered to achieve precise estimates of clearance and volume of distribution for sapropterin dihydrochloride in each age group (birth to <1 years, 1-2 years, 2-4 years and 4-6 years).

Study 2: Safety and Efficacy Study
A minimum of 60 BH4-responsive patients with PKU (responders) will enroll in the Safety and Efficacy Study (Study 2). Of the patients enrolled in the Safety and Efficacy Study (Study 2), at least ten (10) must be less than one year of age, at least twenty (20) must be less than two years of age, 20 patients must be age 2-4 years, and 20 patients must be age 4-6 years at the time of entry into the study.

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:

Study 1: PK-PD and Tolerability Study

Pharmacokinetic Endpoints:
Population PK study will evaluate the population pharmacokinetics (PK) of sapropterin dihydrochloride in young children 0 months to 6 years of age. The sampling time should be optimized to allow adequate characterization of the PK profile. In addition, investigators will be asked to collect a blood sample for total biopterin testing with the occurrence of a serious adverse event, if possible, if it is considered by the investigator to be probably or possibly related to sapropterin dihydrochloride.

Pharmacodynamic Endpoints:
Sapropterin dihydrochloride responsiveness must be assessed by a ≥ 30% decrease in blood Phe from baseline (pretreatment) to the end of the study (e.g., 4 weeks) while on a PKU controlled diet.

Safety Endpoints:
Safety assessments must include adverse events, tolerability, vital signs, laboratory parameters and growth and development parameters. The following adverse events must be actively monitored:

- Changes in liver enzymes.
- All adverse events must be monitored until symptom resolution or until the condition stabilizes.
- The following adverse events must be captured when spontaneously reported: Arrhythmias, syncope, palpitations, chest pain, shortness of breath, cyanosis, paresthesias, and sudden death. All other adverse events must also be captured when spontaneously reported.

Study 2: Safety and Efficacy Study

Efficacy Endpoints:
The primary efficacy endpoint will be effectiveness of sapropterin dihydrochloride treatment over 6 months and must be assessed by the change in blood Phe levels from baseline (no treatment) at the end of 6 months.

Important secondary endpoints must include age appropriate neurocognitive developmental assessments and must be assessed using well-validated and age-appropriate measures, including the Bayley III. Standardized and replicated measurements of head circumference (less than 3 years of age), weight and length/height must be assessed.

Measures of compliance must include diet recording, pill count, and attendance at required study visits.

Safety Endpoints:
Safety outcomes must include adverse events, tolerability, vital signs, laboratory parameters, and growth and development parameters. The following adverse events must be actively monitored:

- Changes in liver enzymes.
- All adverse events must be monitored until symptom resolution or until the condition stabilizes.
- The following adverse events must be captured when spontaneously reported: arrhythmias, syncope, palpitations, chest pain, shortness of breath, cyanosis, paresthesias, and sudden death. All other adverse events must also be captured when spontaneously reported.

Known Drug Safety concerns and monitoring:

Your safety monitoring plan will include a baseline medical history, vital signs, physical examination, including measurements of growth (i.e., height and weight, and head circumference for patients less than two years of age), developmental assessments (e.g., Bayley III, etc.), and clinical laboratory tests (chemistry, hematology, and urinalysis).

Patients will remain at the study site for three hours after receipt of the first dose, with vital signs taken pre-dose, and 15, 30, 45, 60, 90, 120, and 180 minutes post-dose. Electrocardiograms will be performed 2 to 6 hours post-dose (estimated time of maximum concentration). Vital signs include seated systolic blood pressure (SBP) and diastolic blood pressure (DBP) measured in mm Hg, heart rate in beats per minute, respiration rate in breaths per minute, and temperature. Vital signs will be measured weekly for the first month of dosing, then monthly until the completion of the study. Medical history will be taken at the screening visit. Physical examinations will be taken at the Screening, Week 0, Week 4, Month 3 and Month 6 visits. Clinical laboratory tests should be performed weekly for the first month of dosing (except the Week 2 visit), then monthly until the completion of the study. Neurocognitive testing will be performed within 6 weeks after a subject is determined to be sapropterin dihydrochloride responsive and after six months of treatment with sapropterin dihydrochloride in patients less than 2 years of age.

Blood chemistry analysis must include, at minimum, liver enzyme tests, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, and gamma-glutamyl transferase (GGT). Hematology testing must include, at minimum, a complete blood count (CBC), including hemoglobin, hematocrit, platelet count, and white blood cell count (WBC) with differential.

Safety will be assessed by evaluating the number and type of adverse events occurring during the study, and by changes from baseline in vital signs, physical examinations, clinical laboratory testing, and developmental assessment results.

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*
  Fully dissolvable tablets, fully dissolvable powder, or liquid may be administered. Whole tablet formulations are not appropriate for the ages being studied.

- *route of administration*
  Oral

- *regimen*
  Sapropterin dihydrochloride will be administered at a starting dose of 20 mg/kg/day once daily. Dosing adjustments will be made to achieve exposures observed in older pediatric patients, as tolerated.

  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.

Statistical information:

Descriptive analysis of the pharmacokinetic parameters of tetrahydrobiopterin must be provided.

Safety and effectiveness: Provide a statistical test of the null hypothesis that the mean change from baseline in blood Phe levels at the end of the treatment phase equals zero. Use descriptive statistics for other measures.

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 sapropterin dihydrochloride 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 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/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 September 13, 2013. 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) should 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 Jessica Benjamin, Regulatory Project Manager, at 301-796-3924.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
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/

JULIE G BEITZ
10/31/2011