



NDA 022181/S-013

**SUPPLEMENT APPROVAL**  
**FULFILLMENT OF POSTMARKETING COMMITMENT**

BioMarin Pharmaceutical Inc.  
Attention: Barbara Winslow, PhD  
Director, Regulatory Affairs  
105 Digital Drive  
Novato, CA 94949

Dear Dr. Winslow:

Please refer to your Supplemental New Drug Application (sNDA) dated and received September 10, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Kuvan® (sapropterin dihydrochloride).

We acknowledge receipt of your amendments dated November 15, 2013; December 10 and 13, 2013; January 2, 8, 17, and 23, 2014; February 12 and 13, 2014; and March 5, 12, 18, and 21, 2014; and April 21, 2014.

This “Prior Approval” supplemental new drug application provides for a response to the Pediatric Written Request, findings from PKU-015 substudies, and changes to the clinical experience with Kuvan treatment to ensure that labeling content is accurate and reflects current knowledge of the product.

**APPROVAL & LABELING**

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert and text for the patient package insert), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

### **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and immediate container labels that are identical to the carton and immediate-container labels submitted on September 9, 2013, received on September 10, 2013, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 022181/S-013.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

### **FULFILLMENT OF POSTMARKETING REQUIREMENT(S)/COMMITMENT(S)**

We have received your submission dated September 10, 2013, reporting on the following postmarketing commitments listed in the December 13, 2007 approval letter.

PMC 948-1            BioMarin commits to designing and implementing a safety, efficacy, and pharmacokinetics study with Kuvan (sapropterin dihydrochloride) in patients with PKU who are four years of age or younger at study entry. Efficacy is to be assessed by the pharmacodynamic outcome measure of blood phenylalanine levels over a six-month period of treatment. A study protocol will be submitted to CDER by June 14, 2008, for concurrence, and the study will be initiated by December 14, 2008. The final study report for this study will be submitted to CDER by June 14, 2010.

We have reviewed your submission and conclude that the above commitment was fulfilled.

We remind you that there are postmarketing commitments listed in the December 13, 2007 approval letter that are still open.

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Amundson Road  
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

*{See appended electronic signature page}*

Andrew E. Mulberg, M.D., FAAP, CPI  
Deputy Director  
Division of Gastroenterology and Inborn  
Errors Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

ENCLOSURE(S):  
Content of Labeling

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ANDREW E MULBERG  
04/23/2014