DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022181/S-017

SUPPLEMENT APPROVAL

BioMarin Pharmaceutical, Inc.
Attention: Kellee Ratliff, RAC
Senior Manager, Regulatory Affairs
105 Digital Drive
Novato, CA 94949

Dear Ms. Ratliff:

Please refer to your Supplemental New Drug Application (sNDA) dated April 13, 2018 and received on April 16, 2018, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Kuvan (sapropterin dihydrochloride) tablets.

Based on the results from a clinical study that assessed the impact of Kuvan co-administration on the absorption and systemic exposure of orally administered drugs that are P-glycoprotein (P-gp) substrates, this Prior Approval supplemental new drug application provides the following updates to the prescribing information (PI):

- Removal of *in vitro* P-gp findings from section 7 (Drug Interactions) and section 12.3 (Clinical Pharmacology/Pharmacokinetics)
- Inclusion of results from the above-mentioned study in section 12.3 (Clinical Pharmacology/Pharmacokinetics.

APPROVAL & LABELING

We 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.

We note that your submission dated January 9, 2019, includes final printed labeling for your PI and Patient Package Insert.

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 Prescribing Information, 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.

In addition, within 14 days, amend all pending supplemental applications that include 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 Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), 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).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

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, contact LCDR Hong Vu, Regulatory Project Manager, at (301) 796-7401 or Hong.Vu@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Lisa M. Soule, M.D.
Associate Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:
Prescribing Information
Patient Package Insert

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LISA M SOULE
02/01/2019 03:55:56 PM