CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-181

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-181

NDA APPROVAL

BioMarin Pharmaceutical, Inc.
Attention: Amy Waterhouse
Vice President, Regulatory and Government Affairs
105 Digital Drive
Novato, CA 94949

Dear Ms. Waterhouse:

Please refer to your new drug application (NDA) dated May 25, 2007, received May 25, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Kuvan (sapropterin dihydrochloride) 100 mg Tablets.

We acknowledge receipt of your submissions dated July 25, 2007, through December 10, 2007.

This new drug application provides for the use of Kuvan (sapropterin dihydrochloride) Tablets for the reduction of blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin- (BH4-) responsive Phenylketonuria (PKU). Kuvan is to be used in conjunction with a Phe-restricted diet.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format submitted on November 21, 2007.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the November 21, 2007, submitted carton and immediate container labels 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 titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. 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 22-181**." 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.

We remind you of your postmarketing study commitments in your submission dated December 10, 2007. These commitments are listed below.

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.

2. BioMarin commits to designing and implementing a long-term study designed to assess growth and neurocognitive development with treatment with Kuvan (sapropterin dihydrochloride) in patients who are eight years of age or younger at study entry. This study is to include blinded assessments of growth (including standardized measurements of recumbent length or height, weight, and head circumference), and developmental testing (the scales used need to be prospectively agreed upon) at six- to twelve-month intervals over a seven-year period. 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, 2017.

3. BioMarin commits to completing the open-label extension study PKU-008, entitled "A Phase 3b, Multicenter, Open–Label Extension Study of Phenoptin™ in Subjects with Phenylketonuria Who Participated in Studies PKU–004 or PKU–006".[1] Patients who participated in the extension study PKU-004 will be treated under PKU-008 for a minimum of two years of total treatment with Kuvan (sapropterin dihydrochloride). Patient accrual is complete, the two-year cutoff period is to be completed on May 30, 2008, and an interim study report will be submitted to CDER by September 30, 2008. The study is to be completed by September 30, 2009, and a final study report will be submitted to CDER by March 30, 2010.

4. BioMarin commits to designing and implementing a registry of patients with PKU being treated with Kuvan (sapropterin dihydrochloride) that will be established to obtain long-term clinical status information. Information will be collected on patient demographics, specifics of treatment with Kuvan (sapropterin dihydrochloride), clinical status, neurocognitive assessments, growth and development (for patients who are pre-pubertal at the start of treatment), and adverse events. This registry will be designed so that detailed clinical status information is collected at registry entry and on a six- to twelve-month basis for at least 15 years. BioMarin commits to conducting one sub-study within the registry that will evaluate the effect of Kuvan (sapropterin dihydrochloride) on pregnancy and lactation. The registry data will be analyzed at yearly intervals and the results will be submitted in annual reports for IND 69,708. A registry protocol will be submitted to CDER by May 25, 2008, for concurrence, and the registry will be initiated by November 25, 2008. The final study report under this registry will be submitted to CDER by May 25, 2025.

5. BioMarin commits to designing and implementing a thorough QT (TQT) study with Kuvan (sapropterin dihydrochloride) that complies with International Conference on Harmonisation (ICH) E14. The dose of Kuvan (sapropterin dihydrochloride) administered in the TQT study is to be selected so that it results in plasma concentrations that cover the expected high clinical exposure scenario in patients with BH_4-responsive PKU, without compromising study subject safety. This study may be a single-dose, positive- and placebo-controlled,

[1]During clinical development, Kuvan was known as Phenoptin.

cross-over study in healthy volunteers. A study protocol will be submitted to CDER by June 14, 2008, for concurrence, and the study will be initiated by October 14, 2008. The final study report for this study will be submitted to CDER by October 14, 2009.

6. BioMarin commits to analyzing the whole blood samples for *PAH* gene mutations that were collected during the PKU-001 study, entitled "A Phase 2, multicenter, open-label study to evaluate the response to and safety of an 8-day course of Phenoptin™ (sapropterin dihydrochloride) treatment in subjects with phenylketonuria who have elevated phenylalanine levels". These samples are to be analyzed for the purpose of determining whether patients with PKU with specific *PAH* mutations are likely to be responders (by change in blood phenylalanine levels) to treatment with Kuvan (sapropterin dihydrochloride). Blood sample collection is complete, and the final report for this analysis will be submitted to CDER by December 14, 2008.

7. BioMarin commits to completing the open-label study PKU-007, entitled "A Phase 2, Multicenter, Open-label Study to Evaluate the Safety and Efficacy of Phenoptin™ in Subjects with Hyperphenylalaninemia Due to Primary BH4 Deficiency". Patient accrual is complete. The core safety and efficacy portion of this study is complete and patients are continuing in an extension portion. A final study report for this 10-week safety and efficacy portion will be submitted to CDER by June 14, 2008.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments should be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence**."

NDA 22-181 was not referred to an advisory committee for review for the following reasons: The efficacy endpoints were clear and easily measured. The evaluation of safety did not reveal any concerning safety signals with Kuvan administration, and the design and results of the efficacy trials did not pose particular concerns. Kuvan did not have any controversial issues which would have benefited from advisory committee discussion.

PROMOTIONAL MATERIALS

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

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

Please submit one market package of the drug product when it is available.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
HFD-001, Suite 5100
5515 Security Lane
Rockville, MD 20852

REPORTING REQUIREMENTS

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

In addition, submit as Postmarketing 15-day Safety Reports, any adverse event related to neutropenia per reporting regulations 21 CFR 314.80.

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Cristi Stark, Regulatory Project Manager, at (301) 796-1007.

Sincerely,

{See appended electronic signature page}

Dan Shames, M.D.
Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Kuvan (sapropterin dihydrochloride) package insert and patient package insert

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/s/

Daniel A. Shames
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