

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-181**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 22-181

SUPPL #

HFD # 180

Trade Name Kuvan

Generic Name sapropterin dihydrochloride

Applicant Name BioMarin Pharmaceutical, Inc.

Approval Date, If Known 12/13/07

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒

NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒

NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

7-for orphan

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

### **1. Single active ingredient product.**

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1

YES ☐ NO ☐

Investigation #2

YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1

YES ☐ NO ☐

Investigation #2

YES ☐ NO ☐

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #2

IND # YES ☐ NO ☐

Explain:

Page 6

Investigation #1

YES ☐

Explain:

!

!

! NO ☐

! Explain:

Investigation #2

YES ☐

Explain:

!

!

! NO ☐

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐

NO ☐

If yes, explain:

---

---

Name of person completing form: Cristi Stark

Title: Regulatory Health Project Manager

Date: 11/23/07

Name of Office/Division Director signing form: Dan Shames

Title: Deputy Office Director/Acting Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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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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Daniel A. Shames  
12/10/2007 05:39:19 PM

[Trade Name] (sapropterin)

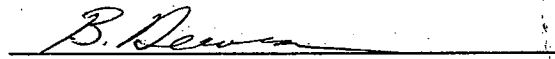
Page 1

**1.3.5.3 EXCLUSIVITY REQUEST**

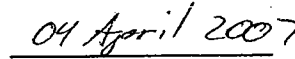
In accordance with Section 527(a) of Food, Drug and Cosmetic Act and Title 21 CFR 316.31, BioMarin Pharmaceutical Inc. claims Orphan Drug Exclusive Approval for {Trade Name}<sup>TM</sup> (sapropterin dihydrochloride). The active pharmaceutical ingredient in {Trade Name}<sup>TM</sup> (sapropterin dihydrochloride) is a new chemical entity.

This product that is the subject of this New Drug Application was granted Orphan Drug Designation on January 29, 2004 (Orphan Designation #03-1815).

Therefore, the Sponsor requests and claims 7 years of market exclusivity following the approval of this New Drug Application.



Ben Dewees  
Senior Manager, Regulatory Affairs  
BioMarin Pharmaceutical Inc.



Date

## PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 22-181 Supplement Type (e.g. SE5): \_\_\_\_\_ Supplement Number: \_\_\_\_\_

Stamp Date: 5/25/07 PDUFA Goal Date: 11/25/07

HFD 180 Trade and generic names/dosage form: Kuvan/Tablets

Applicant: BioMarin Pharmaceutical, Inc. Therapeutic Class: \_\_\_\_\_

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? \*

☒ Yes. Please proceed to the next question.

☐ No. PREA does not apply. Skip to signature block.

*\* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) previously approved (please complete this section for supplements only): N/A

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): \_\_\_\_\_

Indication #1: \_\_\_\_\_

Is this an orphan indication?

☒ Yes. PREA does not apply. Skip to signature block.

☐ No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

☐ Yes: Please proceed to Section A.

☐ No: Please check all that apply: ☐ Partial Waiver ☐ Deferred ☐ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

### Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population

☐ Disease/condition does not exist in children

☐ Too few children with disease to study

☐ There are safety concerns

☐ Other: \_\_\_\_\_

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section B: Partially Waived Studies**

Age/weight range being partially waived (fill in applicable criteria below):

|           |          |           |           |                    |
|-----------|----------|-----------|-----------|--------------------|
| Min _____ | kg _____ | mo. _____ | yr. _____ | Tanner Stage _____ |
| Max _____ | kg _____ | mo. _____ | yr. _____ | Tanner Stage _____ |

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other: \_\_\_\_\_

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

**Section C: Deferred Studies**

Age/weight range being deferred (fill in applicable criteria below):

|           |          |           |           |                    |
|-----------|----------|-----------|-----------|--------------------|
| Min _____ | kg _____ | mo. _____ | yr. _____ | Tanner Stage _____ |
| Max _____ | kg _____ | mo. _____ | yr. _____ | Tanner Stage _____ |

Reason(s) for deferral:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

**Section D: Completed Studies**

Age/weight range of completed studies (fill in applicable criteria below):

|           |          |           |           |                    |
|-----------|----------|-----------|-----------|--------------------|
| Min _____ | kg _____ | mo. _____ | yr. _____ | Tanner Stage _____ |
| Max _____ | kg _____ | mo. _____ | yr. _____ | Tanner Stage _____ |

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

NDA 22-181

Page 3

**This page was completed by:**

*{See appended electronic signature page}*

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**Regulatory Project Manager**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH  
STAFF at 301-796-0700**

**(Revised: 10/10/2006)**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: \_\_\_\_\_

Is this an orphan indication?

- ☐ Yes. PREA does not apply. Skip to signature block.
- ☐ No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.
- ☐ No: Please check all that apply: \_\_\_\_ Partial Waiver \_\_\_\_ Deferred \_\_\_\_ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other: \_\_\_\_\_

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section B: Partially Waived Studies**

Age/weight range being partially waived (fill in applicable criteria below)::

|           |          |           |           |                    |
|-----------|----------|-----------|-----------|--------------------|
| Min _____ | kg _____ | mo. _____ | yr. _____ | Tanner Stage _____ |
| Max _____ | kg _____ | mo. _____ | yr. _____ | Tanner Stage _____ |

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is*

complete and should be entered into DFS.

**Section C: Deferred Studies**

Age/weight range being deferred (fill in applicable criteria below)::

|           |          |           |           |                    |
|-----------|----------|-----------|-----------|--------------------|
| Min _____ | kg _____ | mo. _____ | yr. _____ | Tanner Stage _____ |
| Max _____ | kg _____ | mo. _____ | yr. _____ | Tanner Stage _____ |

Reason(s) for deferral:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

**Section D: Completed Studies**

Age/weight range of completed studies (fill in applicable criteria below):

|           |          |           |           |                    |
|-----------|----------|-----------|-----------|--------------------|
| Min _____ | kg _____ | mo. _____ | yr. _____ | Tanner Stage _____ |
| Max _____ | kg _____ | mo. _____ | yr. _____ | Tanner Stage _____ |

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

\_\_\_\_\_  
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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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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Cristi Stark

11/26/2007 02:34:01 PM

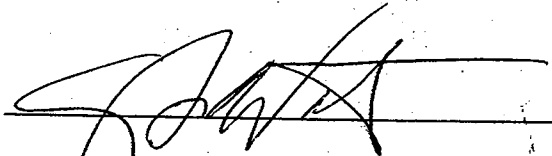
[Trade Name] (sapropterin)

Page 1

### 1.3.3. DEBARMENT CERTIFICATION

Certification Pursuant to Section 306 (k)(1) of the Federal Food, Drug and Cosmetic Act [21 U.S.C. Section 335a (k)(1)].

BioMarin Pharmaceutical Inc. certifies that the services of any person debarred under subsections (a) or (b) of Section 306 of the Federal Food, Drug and Cosmetic Act [21 U.S.C Section 335a (a) or (b)] were not and will not be used in any capacity in connection with this application.



Amy Waterhouse  
Vice President, Regulatory Affairs  
BioMarin Pharmaceutical Inc.

4/19/07  
Date



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 69,708

Biomarin Pharmaceutical, Inc.  
Attention: Steve Harris, M.S., RAC  
Senior Manager, Regulatory Affairs  
105 Digital Drive  
Novato, CA 94949

Dear Mr. Harris:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Phenoptin (6R-tetrahydrobiopterin) Tablets.

We also refer to the meeting between representatives of your firm and the FDA on November 22, 2004. The purpose of the meeting was to discuss development of Phenoptin.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-6416.

Sincerely,

*{See appended electronic signature page}*

Pat Madara  
Regulatory Project Manager  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** November 22, 2004

**TIME:** 1:30 – 3:00 PM

**LOCATION:** Parklawn Building, Chesapeake Conference Room

**APPLICATION:** IND 69,708 Phenoptin (tetrahydrobiopterin)

**TYPE OF MEETING:** Type B; End of Phase 2 Meeting

**MEETING CHAIR:** David G. Orloff, M.D.; Division Director

**MEETING RECORDER:** Pat Madara, Regulatory Project Manager

### FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

#### Division of Metabolic and Endocrine Drug Products (DMEDP)

|                                       |                                                 |
|---------------------------------------|-------------------------------------------------|
| 1. David G. Orloff, M.D.;             | Division Director                               |
| 2. Mary Parks, M.D.;                  | Deputy Director                                 |
| 3. William Lubas, M.D.;               | Medical Officer                                 |
| 4. Karen Davis-Bruno, Ph.D.;          | Pharmacology/Toxicology Supervisor              |
| 5. John Colerangle, DVM, Ph.D., DABT; | Pharmacology/Toxicology Reviewer                |
| 6. Hae Young Ahn, Ph.D.;              | Clinical Pharmacology/Biopharmaceutics Team     |
| Leader                                |                                                 |
| 7. Sang Chung, Ph.D.;                 | Clinical Pharmacology/Biopharmaceutics Reviewer |
| 8. Jon T. Sahlroot, Ph.D.;            | Biometrics Team Leader                          |
| 9. Pat Madara, M.S.;                  | Regulatory Project Manager                      |

#### Office of New Drug Chemistry, Division of New Drug Chemistry II

|                              |                                          |
|------------------------------|------------------------------------------|
| 1. Blair Fraser, Ph.D.;      | Deputy Director                          |
| 2. Sheldon Markofsky, Ph.D.; | Chemistry Team Leader (acting) for DMEDP |
| 3. Yvonne Yang, Ph.D.;       | Chemistry Reviewer for DMEDP             |

**EXTERNAL CONSTITUENT ATTENDEES AND TITLES:****Biomarin Pharmaceutical, Inc.**

- |                                    |                                            |
|------------------------------------|--------------------------------------------|
| 1. Alex Dorenbaum, M.D.,           | Medical Director                           |
| 2. Emil Kakkis, M.D., Ph.D.,       | Senior Vice President, Business Operations |
| 3. _____                           |                                            |
| 4. _____                           |                                            |
| 5. Chuck O'Neill, Ph.D., D.A.B.T., | Director, Toxicology/Pharmacology          |
| 6. Amy Lambert, Ph.D., D.A.B.T.,   | Scientist, Toxicology/Pharmacology         |
| 7. Victoria Sluzky, Ph.D.,         | Senior Director, QC & Analytical Chemistry |
| 8. Steve Jungles,                  | Senior Director, Contract Manufacturing    |
| 9. _____                           |                                            |
| 10. Amy Waterhouse,                | Senior Director, Regulatory Affairs        |
| 11. Scott Harris,                  | Senior Manager, Regulatory Affairs         |

**BACKGROUND:**

Biomarin Pharmaceutical is developing Phenoptin (6R-tetrahydrobiopterin, sapropterin hydrochloride) as a treatment for phenylketonuria (PKU). PKU is an autosomal recessive genetic metabolic disease caused by mutations in the phenylalanine hydroxylase gene (PAH) that leads to elevated levels of phenylalanine (Phe) in the blood, brain, and other tissues. Elevated Phe levels are neurotoxic and result in mental retardation, neurocognitive, and other neuropsychiatric disorders if left untreated. Currently, the only treatment is a highly restrictive, low-Phe diet, beginning at birth. \_\_\_\_\_ is a co-factor for PAH and its administration in pharmacologic doses is associated with variable increases in PAH activity and reductions in Phe blood levels. While not all patients with PKU are found to respond to \_\_\_\_\_ therapy (e.g., those with null mutations who produce no PAH protein), many with partial PAH deficiency do, apparently, respond. Treatment with Phenoptin is expected to moderate the clinical adverse effects associated with dietary indiscretion in patients with PKU, a common problem, particularly when children reach adolescence.

Biomarin has received orphan drug designation for Phenoptin treatment of PKU from the FDA Office of Orphan Products Development.

**Biomarin submitted specific questions for Discussion:****Clinical Questions:**

1. Is long-term reduction in blood Phe levels compared to placebo acceptable as the primary endpoint for assessment of efficacy in the Phase 3 study?

**DMEDP response:**

*Yes, blood phenylalanine levels are an acceptable primary endpoint in the clinical studies submitted to the NDA. However, the division will request that the sponsor submit a plan for post-approval follow up of treated patients to assess long term potential benefits of treatment (e.g., IQ and neuropsychological status).*

2. Is the statistical analysis plan declared in Protocol PKU-003 acceptable?

**DMEDP response:**

*The data should be analyzed by both LOCF and longitudinal methods, however, the primary analysis conducted should be LOCF.*

*The sponsor was asked why "100" and "0" were both to be excluded from the confidence interval for treatment difference and was informed that it was only necessary to exclude "0" in order to demonstrate a statistical difference. The confidence interval will also be examined from a clinical perspective.*

3. Is Protocol PKU-003 adequate as the pivotal protocol for NDA approval?

**DMEDP response:**

*The division feels that studies 003 and 005 may not be adequate to permit labeling with regard to dosing. Therefore, we suggest you redesign study 003 as a placebo controlled trial with a forced titration scheme. Responders could still be defined using the data from study 001 in patients treated with 10mg/kg/day. Patients in the drug group would receive 5mg/kg/day for 2 weeks followed by 10mg/kg/day for 2 weeks and finally 20mg/kg/day for the last 2 weeks. Responders could be randomized to drug or placebo asymmetrically so that more patients would be in the active treatment group. Patients should be stratified depending on whether or not they are on a low Phe diet.*

*The sponsor was asked to include age appropriate prespecified escape criteria in the trial based on blood phenylalanine levels.*

4. Does the Division have any comments regarding the design of the extension study PKU-004 or the dosing study PKU-005?

**DMEDP response:**

*Instead of treating everyone with 10mg/kg/day as originally proposed, it is recommended that the information from the forced dose titration phase, study 003, be used to determine the dose for each patient enrolled in the open label extension trial 004. Alternatively, this open label study can be used by individual physicians to titrate patients to the most effective dose. Since the original trial 003 will be only 6 weeks instead of 12 weeks, it is recommended that this trial is extended to 18 weeks so that there will still be 6 month data available. Age appropriate prespecified escape criteria based on blood phenylalanine level should be included in the trial 004 as well.*

*Study 005 is no longer needed if study 003 is redesigned to include a forced titration.*

5. Is the Daiichi Suntory PK data sufficient for registration?

**DMEDP response:**

*No, the data are not sufficient. We would request a Pk study in pediatric patients and a population PK approach can be considered if there are some limitations for blood samplings or other study conditions for pediatric patients.*

*In addition, since fruit juices can alter the bioavailability of drug, we recommend a bioavailability study be conducted to assure that fruit juices are comparable to water. Alternatively, the drug could be labeled to be dissolved in water only. You can conduct the bioavailability study concurrently with the clinical trials; however, differences in bioavailability between administration with fruit juice and water may affect interpretability of clinical trial results.*

6. Will the quantity and type of data generated from Protocols PKU-001, 003, 004 and 005 provide adequate efficacy information in support of NDA approval?

**DMEDP response:**

*In general, the revised 003 and 004 protocols should supply adequate efficacy information, but any final approval will be dependent on a formal review of the statistical significance and robustness of the clinical response.*

*The division raised the concern that it was currently unknown if BID or TID dosing would result in lower phenylalanine AUC levels than QD dosing, and recommended a small crossover trial to confirm that once daily dosing is equivalent to or more efficacious than BID dosing when comparing phenylalanine AUC at steady state to baseline.*

7. Is the proposed safety database, in addition to data available from the Daiichi Suntory studies, adequate for registration?

**DMEDP response:**

*The sponsor confirmed that they will have a total 400 patients treated for 8 days, 100 for 3 months, and 50 for 6 months in their proposed safety database. This is much lower than recommended in ICH guidelines (i.e. 300-600 pts at 6 months and 100 pts at 1 year). The Division is aware that it is difficult to identify large numbers of patients for orphan drugs and is willing to accept the current numbers of patients if the sponsor proposes an adequate post marketing safety plan to allow accumulation of useful long-term safety information for this chronic indication.*

*The Division also requested that the final safety data be submitted in two parts. Part one would include only PKU patients treated in the clinical trials in the current safety program and part two would include combined safety data on patients treated by the sponsor or Daiichi regardless of indication.*

**Non-clinical Question:**

8. Will the Daiichi Suntory nonclinical studies presented in the IND serve as adequate support for NDA approval?

**DMEDP response:**

*The studies are adequate, however, you should provide evidence to support the similarity in marmoset, rat and human metabolic profiles of Phenoptin.*

*You should also address whether racemization of the R-isomer to S-Phenoptin occurs in vivo in animals and humans and provide a list of the drug batches used in these toxicity studies which includes levels of*

*the S-isomer tested.*

*Address whether Phenoptin crosses the placenta or is secreted into milk.*

- Note: The sponsor stated that data from rats indicated that the drug did not pass into the placenta or breast milk and that it was poorly bioavailable (9-12%). (Also see "additional issues discussed".)

*The safety of pharmacologic doses of tetrahydrobiopterin during postnatal development may be provided by supporting literature. Alternatively additional juvenile animal studies may be useful in assessing any potential long-term developmental delays.*

*The ECAC has found the mouse carcinogenicity study to be inadequate, however, the rat study is considered adequate and no further carcinogenicity studies will be required. The positive chromosome aberration and pheochromocytoma findings were considered treatment related and should be included in the informed consent and product label.*

Chemistry and Manufacturing Questions:

9. Does the Division agree that            is the starting material for the drug substance manufacturing process?

DMEDP response:

\_\_\_\_\_

10. With respect to plans for scaling up the drug substance process, does the Division agree with the plans for demonstrating comparability between the processes?
- The sponsor clarified that a 10-fold scale-up of the manufacturing process and/or identification of an additional manufacturer for the drug substance will be needed for the commercial supply of Phenoptin. Product comparability, between the clinical batches and the ones for commercial use, will be demonstrated.
  - The sponsor indicated that they had determined the crystal structure of Phenoptin.

DMEDP response:

*The proposed plan for the demonstration of product comparability is acceptable, in addition to the tests proposed in the meeting package, we recommend that the sponsor also include:*

- *both proton and carbon-13 NMR for structural identification*
- *adequate proof of structure for BH4, e.g., appropriate information from x-ray crystal structure determination.*

11. Are the proposed drug substance and drug product specification attributes acceptable for registration?

**DMEDP response:**

***Specifications for Drug Substance:***

- *JP methods, instead of USP methods, are used in the specifications for the drug substance. Regulatory methods need to be USP or USP-comparable methods. Please provide a copy of the JP method, and please show if the JP methods are equivalent or better than the USP methods.*
- *The proposed specifications appear to be reasonable for a Phase III study. The acceptability of your acceptance criteria will be determined after evaluation of the data during the NDA review.*

***Specifications for Drug Product:***

- *You should include a dissolution test in the specifications for the drug product. You indicated that a*  

---
- *The acceptability of your acceptance criteria will be determined after examination of the data during the NDA review.*

12. Does the Division agree that the proposed drug substance and drug product stability protocols are acceptable to support product registration?

**DMEDP response:**

*The proposed stability protocol for drug product is acceptable however; you should also include stability testing under accelerated conditions in the proposed stability protocol for drug substance.*

**Regulatory Questions:**

13. Is Fast Track designation reasonable?

**DMEDP response:**

*The sponsor is welcome to seek fast track designation if they believe this application meets the criteria for same.*

14. Would the Division consider issuing a written request for information on children 8 yrs of age and older who will be included in Protocols PKU-001, 003, 004, and 005?

**DMEDP response:**

*The division will consult the pediatric division to see if a written request would be appropriate for this pediatric indication.*  

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Additional issues discussed:

\_\_\_\_\_, once the drug is approved it is likely to be used off label for this indication and there will not be useful dosing information in the label to address this indication. \_\_\_\_\_

\_\_\_\_\_ once the drug is approved it is likely to be used off label for this indication. The sponsor stated that data from rats showed that the drug did not pass into the placenta or breast milk and that it was poorly bioavailable (9-12%). The sponsor proposed setting up a registry to follow patients with maternal PKU post marketing.

- Additional Chemistry Recommendations:

Regarding characterization of the reference standard, please include both proton and carbon-13 NMR and provide adequate proof of structure for BH4.

Please provide information for manufacturing process for the drug product including a flow chart and the in-process controls.

Please provide container/closure information for all proposed packaging presentations including reference to all the Drug Master Files, CFRs (including any food regulations).

At the time of NDA submission, we would like to have 12-month real time and 6-month accelerated stability data, from three primary batches (pilot batches of 1/10 scale acceptable).

At the time of NDA submission, all sites need to be clearly identified and ready for GMP inspection

Please identify all necessary Drug Master Files, and provide copies of Letters of Authorization with the information regarding the volume and page number for the specific item referenced in the Drug Master File.

Please provide supporting data that racemization does not occur during the manufacturing process and storage.

A pre-NDA meeting is recommended before the submission of the NDA.

- The Division would recommend that the 100 mg tablet be scored to permit dosing of 50 mg. (It will be necessary to conduct a dissolution study using scored and unscored tablets to assure comparability.)

**Minutes Preparer:**

Pat Madara  
Regulatory Project Manager  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

**Chair Concurrence:**

David G. Orloff, M.D.  
Division Director  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

Patricia Madara  
12/28/04 03:32:01 PM

## MEMORANDUM OF TELECON

DATE: December 7, 2007

APPLICATION NUMBER: NDA 22-181

BETWEEN:

Name: Mary Jo Bagger  
Amy Waterhouse  
Representing: BioMarin Pharmaceutical, Inc.

AND

Name: Anne Pariser, DGP  
Cristi Stark, DGP

SUBJECT: clinical PMC changes

A short teleconference was held with BioMarin regarding the submission timelines for proposed PMC 3 for the open-label extension study PKU-008. FDA requested an interim study report to be submitted to CDER in 2008 for additional safety data representing a minimum of patients treated with Kuvan for two years. BioMarin proposed a cutoff period of May 30, 2008, with the interim study report submission on September 30, 2008. FDA agreed. BioMarin agreed to submit this updated PMC to the NDA.

The call concluded.

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Cristi Stark, MS  
Regulatory Health Project Manager

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/s/

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Cristi Stark  
12/10/2007 05:26:07 PM

## **Stark, Cristi L**

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**From:** Kowblansky, Marie  
**Sent:** Monday, November 26, 2007 9:39 AM  
**To:** Stark, Cristi L  
**Subject:** FW: Priority NDA 22-181

**Importance:** High

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**From:** Cruz, Concepcion  
**Sent:** Wednesday, November 21, 2007 12:58 PM  
**To:** Rhee, Moo Jhong  
**Cc:** Athey, Linda; Sun, Yichun; Kowblansky, Marie; Friedman, Rick L; Dietrick, John M; Ferguson, Shirnette D; Anderson, Eric W; Henry, James C  
**Subject:** RE: Priority NDA 22-181  
**Importance:** High

Moo Jhong,

OC entered an overall acceptable recommendation in EES. I notified Yichun Sun already.

Happy Thanksgiving to all!

Coki Cruz  
301-827-9013 voice  
301-827-8909 fax

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**From:** Cruz, Concepcion  
**Sent:** Wednesday, November 21, 2007 7:46 AM  
**To:** Rhee, Moo Jhong  
**Cc:** Athey, Linda; Ferguson, Shirnette D  
**Subject:** RE: Priority NDA 22-181  
**Importance:** High

Moo Jhong,

The inspection at BioMarin was ongoing before I left office yesterday. We plan to contact the DO around 11am EST for any update, and enter OC recommendation soon after that.

Please feel free to reach us.

Just in the side, does the RD moving to approve or approvable decision?

Coki Cruz  
301-827-9013 voice  
301-827-8909 fax

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**From:** Young, Rochelle B  
**Sent:** Thursday, November 15, 2007 4:55 PM  
**To:** Henry, James C  
**Cc:** Rhee, Moo Jhong; Cruz, Concepcion; Athey, Linda; Anderson, Eric W

**Subject:** FW: Priority NDA 22-181

**Importance:** High

Jim,

Please read the emails below regarding the above application that needs an inspection. Per EES, the district goal date was set at **January 25, 2008**, with an **User fee goal date of March 25, 2008**.

As you can see from the email below, the review division has an earlier date of November 25, 2007 which is in conflict with the information we received and have set our inspection time table by from EES.

I have reviewed the status of BioMarin and noted that this firm was last inspected 11/06 as an ADE inspection; 2/05 as a biologic inspection; and 11/04 as a biologic inspection. There is no record of the firm having an inspection as a control testing laboratory for drug substance or finished dosage release tester as indicated for this application.

HQ has this NDA as a priority.

Please correspond with Moo-Jhong on the planned course of action. As you know I will be leaving 11/23/07 for an international assignment.

*Rochelle B. Young, RPh, MSA  
Commander, US Public Health Service  
SAN-DO Pre-Approval Manager  
510-337-6804*

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**From:** Athey, Linda  
**Sent:** Thursday, November 15, 2007 1:00 PM  
**To:** Young, Rochelle B  
**Subject:** FW: Priority NDA 22-181

Rochelle,

Moo-Jhong is the CMC Branch Chief and decided to send the email. Please let me know if there is anything else you need.

Thanks,  
Linda

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**From:** Sun, Yichun  
**Sent:** Thursday, November 15, 2007 3:22 PM  
**To:** Athey, Linda; Stark, Cristi L  
**Subject:** FW: Priority NDA 22-181

FYI

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**From:** Rhee, Moo Jhong  
**Sent:** Thursday, November 15, 2007 3:15 PM  
**To:** Friedman, Rick L  
**Cc:** Morefield, Elaine; Chen, Chi-Wan; Nasr, Moheb M; Kowblansky, Marie; Sun, Yichun  
**Subject:** Priority NDA 22-181

Hi Rick,

I have a situation where NDA 22-181, which is due on November 25, 2007, has not received a final recommendation

from your Division. Apparently, the subject facility, which is testing drug product and drug substance, has not been scheduled for inspection yet.

Since this is a priority NDA, I would greatly appreciate it, if you could look into this situation ASAP.

Thanks in advance for your prompt attention.

**Moo-Jhong**

Moo-Jhong Rhee, Ph.D.  
Chief, Branch III  
Pre-Marketing Division II  
Office of New Drug Quality Assessment  
OPS/CDER/FDA  
White Oak Campus, Bldg. 22 Rm 2486  
10903 New Hampshire Ave  
Silver Spring, MD 20993  
Phone 301-796-1440  
moojhong.rhee@fda.hhs.gov

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |         |                                           |                                                                                                                                                                      |                                                      |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|-------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINISTRATION                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |         | <b>REQUEST FOR CONSULTATION</b>           |                                                                                                                                                                      |                                                      |
| TO (Office/Division): <b>PMHS</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |         |                                           | FROM (Name, Office/Division, and Phone Number of Requestor): <b>Cristi Stark, DGP, x61007</b>                                                                        |                                                      |
| DATE<br><b>11/21/07</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | IND NO. | NDA NO.<br><b>22-181</b>                  | TYPE OF DOCUMENT<br><b>NDA - PMCs &amp; WR from IND</b>                                                                                                              | DATE OF DOCUMENT                                     |
| NAME OF DRUG<br><b>sapropterin dihydrochloride</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |         | PRIORITY CONSIDERATION<br><b>priority</b> | CLASSIFICATION OF DRUG                                                                                                                                               | DESIRED COMPLETION DATE<br><b>12/5/07 - PeRC mtg</b> |
| NAME OF FIRM: <b>BioMarin Pharmaceuticals</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |         |                                           |                                                                                                                                                                      |                                                      |
| <b>REASON FOR REQUEST</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |         |                                           |                                                                                                                                                                      |                                                      |
| <b>I. GENERAL</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |         |                                           |                                                                                                                                                                      |                                                      |
| <input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER<br><input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> END-OF-PHASE 2a MEETING <input type="checkbox"/> FINAL PRINTED LABELING<br><input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> END-OF-PHASE 2 MEETING <input type="checkbox"/> LABELING REVISION<br><input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE<br><input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> SAFETY / EFFICACY <input type="checkbox"/> FORMULATIVE REVIEW<br><input type="checkbox"/> MANUFACTURING CHANGE / ADDITION <input type="checkbox"/> PAPER NDA <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):<br><input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> CONTROL SUPPLEMENT |         |                                           |                                                                                                                                                                      |                                                      |
| <b>II. BIOMETRICS</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |         |                                           |                                                                                                                                                                      |                                                      |
| <input type="checkbox"/> PRIORITY P NDA REVIEW <input type="checkbox"/> CHEMISTRY REVIEW<br><input type="checkbox"/> END-OF-PHASE 2 MEETING <input type="checkbox"/> PHARMACOLOGY<br><input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> BIOPHARMACEUTICS<br><input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):<br><input type="checkbox"/> OTHER (SPECIFY BELOW):                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |         |                                           |                                                                                                                                                                      |                                                      |
| <b>III. BIOPHARMACEUTICS</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |         |                                           |                                                                                                                                                                      |                                                      |
| <input type="checkbox"/> DISSOLUTION <input type="checkbox"/> DEFICIENCY LETTER RESPONSE<br><input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS<br><input type="checkbox"/> PHASE 4 STUDIES <input type="checkbox"/> IN-VIVO WAIVER REQUEST                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |         |                                           |                                                                                                                                                                      |                                                      |
| <b>IV. DRUG SAFETY</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |         |                                           |                                                                                                                                                                      |                                                      |
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY<br><input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE<br><input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> POISON RISK ANALYSIS<br><input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP                                                                                                                                                                                                                                                                                                                                                                                                                                                                |         |                                           |                                                                                                                                                                      |                                                      |
| <b>V. SCIENTIFIC INVESTIGATIONS</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |         |                                           |                                                                                                                                                                      |                                                      |
| <input type="checkbox"/> CLINICAL <input type="checkbox"/> NONCLINICAL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |         |                                           |                                                                                                                                                                      |                                                      |
| <b>COMMENTS / SPECIAL INSTRUCTIONS:</b> This consult is to review the posed pediatric PMCs for NDA 22-181 for approval. Also we intend to meet with PeRC to issue a written request. All PMCs and WR material will be sent separately via email to Rosemary Addy by the requested date of 11/28/07.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |         |                                           |                                                                                                                                                                      |                                                      |
| SIGNATURE OF REQUESTOR<br><b>Cristi Stark</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |         |                                           | METHOD OF DELIVERY (Check one)<br><input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND |                                                      |
| PRINTED NAME AND SIGNATURE OF RECEIVER                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |         |                                           | PRINTED NAME AND SIGNATURE OF DELIVERER                                                                                                                              |                                                      |

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/s/

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Cristi Stark

11/21/2007 01:24:53 PM

**M E M O R A N D U M**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**CLINICAL INSPECTION SUMMARY**

DATE: 11/14/2007

TO: Cristi Stark, Project Manager  
Wen-Yi Gao, M.D., Clinical Reviewer  
Division of Gastrointestinal Products, HFD-180

FROM: Khairy Malek, M.D.  
DSI-GCP1

THROUGH: Constance Lewin, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Branch I  
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: # 22-181

APPLICANT: BioMarin Pharmaceutical Inc.

DRUG: Kuvan (phenoptin TM, sapropterin hydrochloride)

THERAPEUTIC CLASSIFICATION: Priority

INDICATION: \_\_\_\_\_

CONSULTATION REQUEST DATE: August 10, 2007

DIVISION ACTION GOAL DATE: November 23, 2007

PDUFA DATE: November 23, 2007

**I. BACKGROUND:**

Phenylketonuria (PKU) is a rare autosomal genetic metabolic disease caused by a mutation in the gene which codes for the conversion of the essential amino acid phenylalanine to tyrosine. There are many degrees of deficiency of the enzyme resulting

in severe or partial deficiency. Current management of PKU includes the use of low-Phe (phenylalanine) diet formula and dietary restriction of Phe-containing foods. BH4 (tetrahydrobiopterin) is a cofactor that binds to form an active intermediate that hydroxylates Phe into tyrosine. Evidence shows that 6R-BH4 tetrahydrobiopterin (sapropterin hydrochloride; phenoptin) can result in a reduction of Phe blood levels in PKU patients.

Two protocols were used in support of this NDA:

Protocol PKU-003 entitled "A Phase 3, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Phenoptin TM in Subjects with Phenylketonuria Who Have Elevated Phenylalanine Levels" and

Protocol PKU-006 entitled "A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Phenoptin TM 20 mg/kg/day to Increase Phenylalanine Tolerance in Phenylketonuric Children on a Phenylalanine-restricted Diet"

Three sites were selected for the inspection of this NDA:

1. Site # 0109 of Barbara Burton, M.D. in Chicago IL: Study PKU-003 and Study PKU-006
2. Site # 0110 of Dorothy Grange, M.D. in St. Louis, MO. : Study PKU-003 and PKU-006
3. Site # 0184 of Daniel Gruskin, M.D. in Decatur, GA: Study PKU-006

#### Summary Report of U.S. Inspections

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#### II. RESULTS (by protocol/site):

| Name of CI and site #, if known | City, State*  | Protocol           | Inspection Date   | EIR Received Date | Final Classification |
|---------------------------------|---------------|--------------------|-------------------|-------------------|----------------------|
| Barbara Burton, MD-Site 0109    | Chicago, IL   | PKU-003<br>PKU-006 | 9/25-<br>19/05/07 | 10/9/07           | NAI                  |
| Dorothy Grange, MD-Site 0110    | St. Louis, MO | PKU-003<br>PKU-006 | 9/17-<br>9/19/07  | 11/8/07           | NAI                  |
| Daniel Gruskin, MD-Site 0184    | Decatur, GA   | PKU-006            | 10/18-<br>11/2    | Pending           |                      |

#### Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

1. Barbara K. Burton, M.D., Children's Memorial Hospital, Chicago, IL-Site # 0109:
  - a. At this site, 6 subjects were enrolled in protocol PKU-003 and all completed the study. Thirteen subjects were enrolled in Part 1 of protocol PKU-006 and all completed the study. Eight subjects completed part 2 of the study
  - b. The field investigator reviewed all the records of the study and there were no limitations of the inspection.
  - c. The inspection revealed minor violations which were mainly that the 2.5-5 hours required by the protocols between a meal and withdrawing blood samples were sometimes exceeded or reduced by about half an hour. This violation did not affect the NAI classification.
  - d. The data from this site are acceptable and can be used in support of the NDA
2. Dorothy K. Grange, M.D., St. Louis, MO-Site # 0110:
  - a. At this site, 2 subjects enrolled and completed protocol PKU-003. Eleven subjects enrolled in protocol PKU-006, of these 5 subjects were randomized to part 2.
  - b. The field investigator reviewed the records of all subjects enrolled in the study and there were no limitations of the inspection.
  - c. The inspection revealed no violations of the federal regulations.
  - d. The data from this site are acceptable and can be used in support of the NDA.
3. Daniel J. Gruskin, M.D., Decatur, GA-Site # 0184-Protocol PKU-006 only
  - a. At this site 10 subjects enrolled and completed part 1. Seven of these completed part 2.
  - b. The field investigator reviewed all the records of the enrolled subjects. There were no limitations of the inspection except that the CI moved out of the area.
  - c. The inspection revealed few protocol violations: Subjects #6100 and #6052 had their mean blood phe in the 6 months before enrollment within the protocol required level of 480 umol/L. However, at screening subject #6100 had a value of 605 umol/L and subject # 6052 had a value of 616 umol/L.

Subject # 6053 had a history of asthma but it was not clear if he/she had oral steroid-dependent asthma as the protocol exclusion criteria specify. The subject asthma worsened during the study and required inhalation therapy. The subject was not discontinued from the study.

- d. The data from this site are acceptable and can be used in support of the NDA.

### III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Inspection of the above three sites reveals that the data from these sites are acceptable and can be used in support of the NDA.

{See appended electronic signature page}

Khairy W. Malek, M.D., Ph.D.  
Medical Officer

#### CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Branch I  
Division of Scientific Investigations

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/s/

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Constance Lewin

11/15/2007 03:40:57 PM

MEDICAL OFFICER

Entered into DFS on behalf of Dr. Khairy Malek  
in his absence.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 69,708

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

Dear Mr. Dewees:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the Act) for Phenoptin<sup>TM</sup> (sapropterin dihydrochloride, 6R-BH4, tetrahydrobiopterin).

We also refer to the meeting between representatives of your firm and the FDA on October 12, 2006. The purpose of the meeting was to discuss BioMarin's phase 3 study results and the adequacy and acceptability of their chemistry, manufacturing, and controls (CMC), clinical, and nonclinical data.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0846.

Sincerely,

*{See appended electronic signature page}*

Ryan Barraco  
Regulatory Project Manager  
Division of Gastroenterology  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure

Meeting Minutes

**Meeting Type:** B  
**Meeting Category:** Pre-NDA  
**Meeting Date and Time:** October 12, 2006; 2:30 – 3:00 PM  
**Meeting Location:** White Oak, Building 22  
**Application Number:** IND 69,708  
**Product Name:** Phenoptin (sapropterin dihydrochloride;  
tetrahydrobiopterin)  
**Received Briefing Package** September 12, 2006  
**Sponsor Name:** BioMarin Pharmaceutical, Inc.  
**Meeting Requestor:** Mr. Ben Dewees  
**Meeting Chair:** Dr. Anne Pariser  
**Meeting Recorder:** Mr. Ryan Barraco  
**Meeting Attendees:**

**FDA Attendees**

Brian E. Harvey, M.D., Ph.D., Division Director, Division of Gastroenterology Products (DGP)  
Joyce Korvick, M.D., M.P.H., Deputy Division Director, DGP  
Anne Pariser, M.D., Medical Team Leader, DGP  
Ethan Hausman, M.D., Medical Officer, DGP  
Ryan Barraco, Regulatory Project Manager, DGP  
Jasti Choudary, B.V.Sc., Ph.D., Supervisory Pharmacologist, DGP  
Stella Grosser, Ph.D., Biometrics Team Leader, Division of Biometrics III  
Marie Kowblansky, Ph.D., Pharmaceutical Assessment Leader, Office of New Drug Quality Assessment  
Zei Pao Huang, Regulatory Review Support Staff  
Paul Maher, M.D., Medical Reviewer, Orphan Product Development (OPD)  
Lisa Mathis, M.D., Director, Pediatric and Maternal Health Staff (PMHS)  
Felicia Collins, M.D., Medical Officer, PMHS

**Sponsor Attendees (BioMarin Pharmaceutical, Inc.)**

Emil Kakkis, M.D., Ph.D., Chief Medical Officer  
Alex Dorenbaum, M.D., Director, Clinical Affairs  
Amy Waterhouse, Vice President, Regulatory Affairs  
Mary Newman, M.S., Senior Director, Regulatory Affairs  
Arthur A. Blum, Sr. Director, Regulatory Affairs  
Ruhi Ahmed, Ph.D., Senior Manager, Regulatory Affairs  
Ben Dewees, Senior Manager, Regulatory Affairs  
Robert Baffi, Ph.D., Senior Vice-President, Technical Operations  
Victoria Sluzky, Ph.D., Vice President, Quality and Analytical Chemistry  
Steve Jungles, Vice President, Supply Chain and Contract Manufacturing  
Dan Oppenheimer, Ph.D., Sr. Director, Product Development

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## 1.0 BACKGROUND

BioMarin Pharmaceutical, Inc. submitted IND 69,708/ Phenoptin<sup>TM</sup> on August 13, 2004. The sponsor is currently conducting their phase 3 clinical investigations and plans to submit their New Drug Application (NDA) in 2007. Phenoptin's proposed indication is reduction of phenylalanine (Phe) in patients with phenylketonuria (PKU) who have hyperphenylalaninemia (HPA). BioMarin received orphan drug designation on January 26, 2004, for tetrahydrobiopterin (sapropterin dihydrochloride) and Phenoptin was designated a fast track product on January 18, 2006. The sponsor submitted a meeting request on July 27, 2006 to discuss BioMarin's phase 3 study results and the adequacy and acceptability of their chemistry, manufacturing, and controls (CMC), clinical, and nonclinical data. In particular, the sponsor wished to discuss the following clinical protocols:

| <u>Study Number (phase)</u>    | <u>Study Objectives</u>                                                                                                                                                                                                                 |
|--------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PKU-003 (phase 3)              | Establish safety and efficacy of 10 mg/kg/day PO or placebo for 6 weeks                                                                                                                                                                 |
| PKU-004 (phase 3)              | <ul style="list-style-type: none"><li>• Evaluate effect of doses of 5-20 mg/kg/day (forced titration) on blood Phe response</li><li>• Obtain 22 weeks exposure safety data</li></ul>                                                    |
| <u>Study Number (phase)</u>    | <u>Study Objectives</u>                                                                                                                                                                                                                 |
| PKU-004 Sub-Study 02 (phase 3) | Establish safety and persistence of Phe control over a 24-hour period on once daily BH4                                                                                                                                                 |
| PKU-001 (phase 2)              | <ul style="list-style-type: none"><li>• Evaluate safety in broad PKU population</li><li>• Evaluate Phe response to an 8-day course of 10 mg/kg/day BH4 PO</li><li>• Identify BH4 responsive subjects for PKU003 participation</li></ul> |
| PKU-001 Sub-Study 01 (phase 1) | Establish safety and persistence of Phe control over a 24-hour period on once daily BH4                                                                                                                                                 |

The projected meeting outcome was for the FDA to provide comprehensive and meaningful responses to BioMarin's questions.

## 2.0 DISCUSSION

1. BioMarin proposes to submit separate ISS documents for the Daiichi Asubio clinical study data and the BioMarin Pharmaceutical study data. Is this acceptable to the Agency?

**Response:**

No. Phenoptin™ (sapropterin dihydrochloride; tetrahydrobiopterin; BH<sub>4</sub>) and Biopten® appear to be the same molecular species, and we require a single integrated summary of safety (ISS) be submitted for review for your NDA according to 21 CFR 314.50 (d) (5) (vi) (a). We agree that pooling safety data between different treatment groups may be inappropriate; however, different sections of your ISS may include data and discussion on the use of sapropterin in different disease states.

2. Does the Agency agree with the conceptual design of a surveillance program to assess long-term potential benefits of treatment?

**Response:**

Your objectives are generally appropriate. We have the following additional recommendations:

You may conduct a sub-study within the registry in patients less than four years of age at their time of entry; however, a separate clinical study of safety, pharmacokinetics, and efficacy in patients less than four years of age should be performed. Endpoints are to include both short- and long-term evaluations including blood phenylalanine (PHE) levels, neurocognitive development, and growth parameters, among other. See response to question 4.

Phenoptin will be administered to patients over a period of time of great physical, physiological, and psychological development; therefore, your Post Marketing Surveillance Program should extend for at least 15 years, so that the youngest patients enrolled will have the opportunity to be formally studied from near birth through puberty. Ideally, all patients entering the registry at less than eight years of age should be followed through age 15 years for potential long-term trends in blood PHE levels, and neurocognitive and other developmental milestones.

An alternative approach would be for you to convert your proposed safety surveillance program for Phenoptin into a clinical trial that: (1) includes neurocognitive endpoints as a primary objective; (2) specifies a minimum number of patient participants needed to ensure meaningful results; and (3) ensures that pediatric subpopulation analyses are consistent with clinically relevant treatment groups per experts in the field. Collection of these data in a clinical trial will permit rigorous collection of high quality data. It is

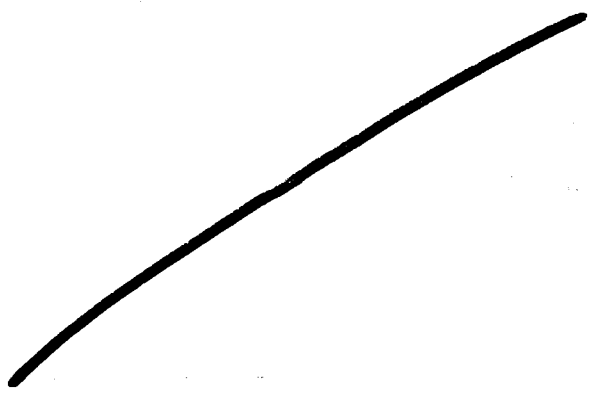
recommended that the detailed clinical protocol be submitted to us for our review before it is initiated.

A pregnancy sub-registry within your registry is recommended. It is anticipated this drug will be used in pregnant women; therefore, you should initiate this pregnancy sub-registry as soon as possible.

3. Will the Division issue a Written Request for sapropterin dihydrochloride based on PKU-006, as permitted under FDC Act § 505A?

**Response:**

Prior to issuing a Written Request (WR), we recommend that you submit a Proposed Pediatric Study Request (PPSR) for the use of Phenoptin as adjunctive therapy to a PHE-restricted diet in pediatric patients with BH<sub>4</sub>-responsive PKU, ages newborn to eight years. To support safe and effective use and dosing of BH<sub>4</sub> in this pediatric population, the study should include pharmacokinetic, safety, and efficacy studies using randomized and blinded protocols similar to those in the pivotal studies.



Please note that pediatric data submitted prior to the issuance of a WR cannot be used to obtain pediatric exclusivity. Please refer to the guidance titled, "Guidance for Industry – Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act."

4. Does the Agency find the filing plan for clinical information acceptable for our NDA submission?

**Response:**

At the time of submission of your NDA, the indication you intend to request should be fully supported by the data submitted to your application. Currently, your briefing packet states that you plan to submit data limited to studies in patients with traditional PKU, age eight years and older, who respond to

Phenoptin as determined by reduction in blood PHE levels. We have the following comments regarding your clinical development program:

To date, Phenoptin has not been studied in children younger than eight years of age. Study PKU-006 proposes to evaluate children ages four through 12 years. Since Phenoptin is likely to be used in this age group, you would need to conduct clinical safety and efficacy study (ies) in these children. These studies should include long-term evaluation of neurocognitive development and other developmental achievements, and should be initiated at the earliest possible time. In addition, since Phenoptin will likely be used in children from time of newborn diagnosis through four years of age, your clinical development plan should include a separate clinical study of the pharmacokinetics, safety, and efficacy of Phenoptin in children four years and younger (see question 2, above).

Your drug is intended for chronic, potentially life-long administration. To date, short-term safety and efficacy studies (i.e., eight days) have been performed in 490 patients, and one study up to six weeks has been completed in 88 responders. These data are insufficient to define the safety profile of your drug. At minimum, at the time of filing, safety and efficacy data from completed Study PKU-004 through Week 26 of the extension study is to be submitted. Open-label, long-term extension study (ies) (i.e., up through at least two years of drug treatment) should be in progress at the time of submission.

Summary of Discussion:

*The Division agrees with the information presented on slide 2 of the Sponsor's presentation along with the qualifier that at the time of NDA submission all of the data should be included for the Study PKU-004 through Week 26.*

5.

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Response:

The proposed starting materials are acceptable, provided you have reasonable specifications.

6. BioMarin is proposing two drug substance manufacturers for sapropterin dihydrochloride [redacted]. Is the proposed comparability protocol approach acceptable to the Agency for demonstrating comparability of drug substance manufactured at the two sites? Moreover, does the Agency agree that if comparability of drug substance manufactured at [redacted] is demonstrated, BioMarin can use drug substance manufactured at either site for producing drug product?

**Response:**

**Your approach for demonstrating comparability of drug substance from the two manufacturers is generally acceptable. However, your proposed drug specifications show that different residual solvents are expected to be present in drug substance from the two sources, indicating that different purification processes are used. Before you can use the materials interchangeably, you will need to provide data showing that the stability of product made with drug substance from all proposed sources compares favorably with product used in clinical trials. Specifically, comparative three-month accelerated stability data should be submitted.**

7. Does the Agency agree that the proposed API stability package is sufficient for the initial NDA filing, and that stability updates can be provided during the review process?

**Response:**

**Your proposed API stability package for NDA filing is acceptable, as is your proposal to supplement the NDA with additional stability data during the review cycle. In order to facilitate a timely review of your application, all data should be included in your NDA at the time of submission.**

8. BioMarin is proposing two drug product manufacturers for sapropterin dihydrochloride tablets ( [REDACTED] Lyne Laboratories Inc.). Is the proposed comparability protocol approach acceptable to the Agency for demonstrating comparability of drug product manufactured at the two sites using the drug substance manufactured at either [REDACTED]

**Response:**

**Your proposed approach is generally acceptable. However, the demonstration of comparability of drug product from the two manufacturers should include at least three months of accelerated and real-time stability data. The critical factor to consider is that the evaluations provide a linkage between the properties of the product used in clinical trials and the product that is produced at the proposed manufacturing sites. If the clinical samples were produced by [REDACTED] and the proposed commercial process will use [REDACTED] you will need to provide a linkage through bioequivalence studies. However, if you can demonstrate that the drug substance is categorized as a Class I material in the Biopharmaceutics Classification System (BCS) system, the bioequivalence studies will not be necessary.**

**Summary of Discussion:**

*The sponsor will provide a clear linkage between clinical trial materials and the commercial batches to demonstrate they are equivalent and eliminate the need for bioequivalence studies.*

9. Does the agency agree that the proposed stability package for drug product is sufficient for the initial NDA application, and that stability updates can be provided during the review process? Moreover, does the agency agree that the combination of supportive stability data on clinical drug product (24 months at controlled room temperature and 6 months at 40°C) and on-going stability testing of registration and commercial drug product support a \_\_\_\_\_ expiry date?

**Response:**

No. While it is acceptable to update your submission with stability data while the NDA is under review, the stability package you intend to provide, with only zero to three months of stability data at the time of submission will not be sufficient. You will need to submit a minimum of three months of stability data at the time of submission for product prepared by the proposed two product manufacturers, Lyne \_\_\_\_\_

The 24-month stability data for product prepared at \_\_\_\_\_ may or may not be useful as supporting data since the data are for product manufactured by a different manufacturer, using drug substance from a different supplier \_\_\_\_\_ using a different manufacturing process \_\_\_\_\_ instead \_\_\_\_\_, and stored in different packaging. This will be determined at the time of NDA review.

10. BioMarin is currently experiencing difficulty with successfully debossing sapropterin dihydrochloride tablets. In order to not delay filing of the NDA, BioMarin would like to review with the Agency the potential for an exemption from code imprinting on tablets as required per 21CFR 206.10. Will the Agency grant BioMarin's request for exemption from 21CFR 206.10, and allow sapropterin dihydrochloride tablets to be manufactured without a code imprint?

**Response:**

No. Per 21 CFR 206.7 an exemption from imprinting can only be given upon showing that the product's size, shape, texture, or physical characteristics make imprinting technologically infeasible or impossible. The information that you have provided in the meeting package does not demonstrate this. If you have additional evidence and arguments to demonstrate that debossing is technologically infeasible or impossible for your product, you should provide it in a separate submission prior to filing your NDA.

**Summary of Discussion:**

***Being that there are only minor changes to the formulation, the general approach to demonstrating comparability of the tablets was acceptable.***

11. Does the Agency agree with BioMarin's proposed filing strategy for the CMC sections of the NDA application?

**Response:**

**When you submit your NDA, it is important to present data that will link the critical properties of the proposed commercial product to the product used in clinical trials: the effects of different manufacturers of drug substance, different manufacturers of drug product, and different manufacturing procedures must be clearly documented.**

12. Is the Nonclinical filing plan acceptable to the Agency?

**Response:**

**Yes, your planned listing of the nonclinical studies is acceptable.**

13. BioMarin is planning to submit the data tabulation datasets in CDISC SDTM format, with the data definition tables and annotated case report form provided in PDF format (define.pdf and blankcrf.pdf). Is this acceptable?

**Response:**

**We currently support the CDISC SDTM Version 3.1.1. We recommend that you submit a sample datasets for evaluation. The purpose of this is to ensure that the submission datasets follows the CDISC SDTM implementation guidance and ensure the SDTM datasets can be loaded to our system. Please visit <http://www.cdisc.org/publications/index.html> to locate the implementation guide. After the sample datasets pass the evaluation, submit the datasets in CDISC SDTM format.**

14. BioMarin is proposing to submit analysis datasets and non-executable analysis programs for primary and secondary endpoints and key safety analyses. Is this acceptable?

**Response:**

**We recommend that you contact with our Electronic Submission Coordinator, Ken Edmunds, to resolve some outstanding issues related to the sample eCTD.**

15. Are there any unpublished dataset requirements of which BioMarin should be aware?

**Response:**

Please clarify your concerns with this issue.

16. Does the Agency have any specific questions regarding the planned electronic NDA in eCTD format for Phenoptin?

**Response:**

Not at this time.

**Additional Comments:**

- If you believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then you are encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).
- For the most recent publicly available information on CDER's views on RiskMAPs, please refer to the following Guidance documents:

Premarketing Risk Assessment:

<http://www.fda.gov/cder/guidance/6357fnl.htm>

Development and Use of Risk Minimization Action Plans:

<http://www.fda.gov/cder/guidance/6358fnl.htm>

Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment: <http://www.fda.gov/cder/guidance/6359OCC.htm>

- If there is any information on product medication errors from the premarketing clinical experience, OSE requests that this information be submitted with the NDA application.
- You are encouraged to submit all associated labels and labeling for review as soon as available.

**Additional Discussion:**

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*The Division reminded the sponsor that all age groups will need to be adequately supported for efficacy and safety.*

**3.0 ISSUES REQUIRING FURTHER DISCUSSION**  
There are not any issues that require further discussion

**4.0 ACTION ITEMS**

| Action Item/Description                                                                                                                                                   | Owner    | Due Date    |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|-------------|
| Include all of the data for Study PKU-004 through Week 26 at the time of NDA submission.                                                                                  | BioMarin | No Due Date |
| Provide a clear linkage between clinical trial materials and the commercial batches to demonstrate they are equivalent and eliminate the need for bioequivalence studies. | BioMarin | No Due Date |
| Contact the Electronic Submission Coordinator, Ken Edmunds, to resolve some outstanding issues related to the sample eCTD.                                                | BioMarin | No Due Date |

**5.0 ATTACHMENTS AND HANDOUTS**  
The sponsor's presentation slides are attached

13 Page(s) Withheld

✓ Trade Secret / Confidential

       Draft Labeling

       Deliberative Process

Withheld Track Number: Administrative-4

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Ryan Barraco  
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Anne Pariser  
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| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINISTRATION                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |         |                                           | <h2 style="margin: 0;">REQUEST FOR CONSULTATION</h2>                                                                                                                                                                     |                                                    |
| TO (Division/Office):<br><b>CDER OSE CONSULTS</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |         |                                           | FROM: Cristi Stark<br>Division of Gastroenterology Products<br>301-796-1007                                                                                                                                              |                                                    |
| DATE<br>10/18/07                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | IND NO. | NDA NO.<br>22-181                         | TYPE OF DOCUMENT<br>New NDA                                                                                                                                                                                              | DATE OF DOCUMENT<br>May 25, 2007                   |
| NAME OF DRUG<br><b>Kuvan (sapropterin dihydrochloride) Tablets</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |         | PRIORITY CONSIDERATION<br><b>Priority</b> | CLASSIFICATION OF DRUG<br><b>In-born Error in Metabolism</b>                                                                                                                                                             | DESIRED COMPLETION DATE<br><b>November 1, 2007</b> |
| NAME OF FIRM: <b>BioMarin Pharmaceutical, Inc.</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |         |                                           |                                                                                                                                                                                                                          |                                                    |
| <b>REASON FOR REQUEST</b><br><b>I. GENERAL</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |         |                                           |                                                                                                                                                                                                                          |                                                    |
| <div style="display: flex; flex-wrap: wrap;"> <div style="width: 33%;"> <input type="checkbox"/> NEW PROTOCOL<br/> <input type="checkbox"/> PROGRESS REPORT<br/> <input type="checkbox"/> NEW CORRESPONDENCE<br/> <input type="checkbox"/> DRUG ADVERTISING<br/> <input type="checkbox"/> ADVERSE REACTION REPORT<br/> <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION<br/> <input type="checkbox"/> MEETING PLANNED BY         </div> <div style="width: 33%;"> <input type="checkbox"/> PRE--NDA MEETING<br/> <input type="checkbox"/> END OF PHASE II MEETING<br/> <input type="checkbox"/> RESUBMISSION<br/> <input type="checkbox"/> SAFETY/EFFICACY<br/> <input type="checkbox"/> PAPER NDA<br/> <input type="checkbox"/> CONTROL SUPPLEMENT         </div> <div style="width: 33%;"> <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER<br/> <input type="checkbox"/> FINAL PRINTED LABELING<br/> <input type="checkbox"/> LABELING REVISION<br/> <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE<br/> <input type="checkbox"/> FORMULATIVE REVIEW<br/> <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): <b>Trade name review</b> </div> </div> |         |                                           |                                                                                                                                                                                                                          |                                                    |
| <b>II. BIOMETRICS</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |         |                                           |                                                                                                                                                                                                                          |                                                    |
| STATISTICAL EVALUATION BRANCH<br><br><input type="checkbox"/> TYPE A OR B NDA REVIEW<br><input type="checkbox"/> END OF PHASE II MEETING<br><input type="checkbox"/> CONTROLLED STUDIES<br><input type="checkbox"/> PROTOCOL REVIEW<br><input type="checkbox"/> OTHER (SPECIFY BELOW):                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |         |                                           | STATISTICAL APPLICATION BRANCH<br><br><input type="checkbox"/> CHEMISTRY REVIEW<br><input type="checkbox"/> PHARMACOLOGY<br><input type="checkbox"/> BIOPHARMACEUTICS<br><input type="checkbox"/> OTHER (SPECIFY BELOW): |                                                    |
| <b>III. BIOPHARMACEUTICS</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |         |                                           |                                                                                                                                                                                                                          |                                                    |
| <input type="checkbox"/> DISSOLUTION<br><input type="checkbox"/> BIOAVAILABILITY STUDIES<br><input type="checkbox"/> PHASE IV STUDIES                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |         |                                           | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE<br><input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS<br><input type="checkbox"/> IN-VIVO WAIVER REQUEST                                                             |                                                    |
| <b>IV. DRUG EXPERIENCE</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |         |                                           |                                                                                                                                                                                                                          |                                                    |
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL<br><input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES<br><input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)<br><input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |         |                                           | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY<br><input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE<br><input type="checkbox"/> POISON RISK ANALYSIS                                  |                                                    |
| <b>V. SCIENTIFIC INVESTIGATIONS</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |         |                                           |                                                                                                                                                                                                                          |                                                    |
| <input type="checkbox"/> CLINICAL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |         |                                           | <input type="checkbox"/> PRECLINICAL                                                                                                                                                                                     |                                                    |
| COMMENTS/SPECIAL INSTRUCTIONS: The Division of Gastroenterology has received a new NDA, Kuvan (sapropterin dihydrochloride) Tablets. An initial tradename review had been completed by DMETS in which Kuvan was found acceptable. We respectfully request another tradename review (the first expired) prior to action. The PDUFA goal date is November 25, 2007. The NDA is available electronically on the EDR at the following link: \\CDSESUB1\EVSPROD\NDA022181. Please contact me if you have any questions.<br><br><b>PDUFA DATE: 11/25/07</b><br><b>ATTACHMENTS:</b> Draft Package Inset, Container and Carton Labels<br><b>CC:</b> Archival IND/NDA<br>HFD-180/Division File<br>HFD-180/RPM<br>HFD-180/Reviewers and Team Leaders                                                                                                                                                                                                                                                                                                                                                                                                                                       |         |                                           |                                                                                                                                                                                                                          |                                                    |
| NAME AND PHONE NUMBER OF REQUESTER                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |         |                                           | METHOD OF DELIVERY (Check one)                                                                                                                                                                                           |                                                    |

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| SIGNATURE OF RECEIVER      | SIGNATURE OF DELIVERER                                                                                   |

5/28/05

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Cristi Stark  
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| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINISTRATION                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |         |                                       | <b>REQUEST FOR CONSULTATION</b>                                                                                                                                      |                                            |
| TO (Office/Division): <b>OND/ QT IRT</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |         |                                       | FROM (Name, Office/Division, and Phone Number of Requestor):<br><b>Marlene G Swider OND/ODEIII/DGP (301) 796-2104</b>                                                |                                            |
| DATE<br><b>10/12/07</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | IND NO. | NDA NO.<br><b>22-181</b>              | TYPE OF DOCUMENT<br><b>New Molecular Entity</b>                                                                                                                      | DATE OF DOCUMENT<br><b>5/25/07</b>         |
| NAME OF DRUG<br><b>Kuvan (sapropterin)</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |         | PRIORITY CONSIDERATION<br><b>ASAP</b> | CLASSIFICATION OF DRUG<br><b>monoclonal</b>                                                                                                                          | DESIRED COMPLETION DATE<br><b>11/12/07</b> |
| NAME OF FIRM: <b>BioMarin</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |         |                                       |                                                                                                                                                                      |                                            |
| <b>REASON FOR REQUEST</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |         |                                       |                                                                                                                                                                      |                                            |
| <b>I. GENERAL</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |         |                                       |                                                                                                                                                                      |                                            |
| <div style="display: flex; flex-wrap: wrap;"> <div style="width: 33%;"> <input type="checkbox"/> NEW PROTOCOL<br/> <input type="checkbox"/> PROGRESS REPORT<br/> <input type="checkbox"/> NEW CORRESPONDENCE<br/> <input type="checkbox"/> DRUG ADVERTISING<br/> <input type="checkbox"/> ADVERSE REACTION REPORT<br/> <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION<br/> <input type="checkbox"/> MEETING PLANNED BY         </div> <div style="width: 33%;"> <input type="checkbox"/> PRE-NDA MEETING<br/> <input type="checkbox"/> END-OF-PHASE 2a MEETING<br/> <input type="checkbox"/> END-OF-PHASE 2 MEETING<br/> <input type="checkbox"/> RESUBMISSION<br/> <input type="checkbox"/> SAFETY / EFFICACY<br/> <input type="checkbox"/> PAPER NDA<br/> <input type="checkbox"/> CONTROL SUPPLEMENT         </div> <div style="width: 33%;"> <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER<br/> <input type="checkbox"/> FINAL PRINTED LABELING<br/> <input type="checkbox"/> LABELING REVISION<br/> <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE<br/> <input type="checkbox"/> FORMULATIVE REVIEW<br/> <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):         </div> </div> |         |                                       |                                                                                                                                                                      |                                            |
| <b>II. BIOMETRICS</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |         |                                       |                                                                                                                                                                      |                                            |
| <div style="display: flex; flex-wrap: wrap;"> <div style="width: 50%;"> <input type="checkbox"/> PRIORITY P NDA REVIEW<br/> <input type="checkbox"/> END-OF-PHASE 2 MEETING<br/> <input type="checkbox"/> CONTROLLED STUDIES<br/> <input type="checkbox"/> PROTOCOL REVIEW<br/> <input type="checkbox"/> OTHER (SPECIFY BELOW):         </div> <div style="width: 50%;"> <input type="checkbox"/> CHEMISTRY REVIEW<br/> <input type="checkbox"/> PHARMACOLOGY<br/> <input type="checkbox"/> BIOPHARMACEUTICS<br/> <input type="checkbox"/> OTHER (SPECIFY BELOW):         </div> </div>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |         |                                       |                                                                                                                                                                      |                                            |
| <b>III. BIOPHARMACEUTICS</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |         |                                       |                                                                                                                                                                      |                                            |
| <div style="display: flex; flex-wrap: wrap;"> <div style="width: 50%;"> <input type="checkbox"/> DISSOLUTION<br/> <input type="checkbox"/> BIOAVAILABILITY STUDIES<br/> <input type="checkbox"/> PHASE 4 STUDIES         </div> <div style="width: 50%;"> <input type="checkbox"/> DEFICIENCY LETTER RESPONSE<br/> <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS<br/> <input type="checkbox"/> IN-VIVO WAIVER REQUEST         </div> </div>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |         |                                       |                                                                                                                                                                      |                                            |
| <b>IV. DRUG SAFETY</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |         |                                       |                                                                                                                                                                      |                                            |
| <div style="display: flex; flex-wrap: wrap;"> <div style="width: 50%;"> <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL<br/> <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES<br/> <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)<br/> <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         </div> <div style="width: 50%;"> <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY<br/> <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE<br/> <input type="checkbox"/> POISON RISK ANALYSIS         </div> </div>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |         |                                       |                                                                                                                                                                      |                                            |
| <b>V. SCIENTIFIC INVESTIGATIONS</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |         |                                       |                                                                                                                                                                      |                                            |
| <div style="display: flex; justify-content: space-between;"> <input checked="" type="checkbox"/> CLINICAL         <input type="checkbox"/> NONCLINICAL       </div>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |         |                                       |                                                                                                                                                                      |                                            |
| <b>COMMENTS / SPECIAL INSTRUCTIONS:</b><br>1. Do you recommend that a thorough QT (TQT) or other cardiac safety study or evaluation be performed for sapropterin?<br>2. If yes, we anticipate that this study would be requested as a post-marketing commitment. Is the performance of a TQT (or other cardiac safety study or evaluation) as a post-marketing commitment reasonable or should a TQT or other evaluation be performed prior to approval?<br>3. If a TQT or other cardiac safety study/evaluation is recommended, please provide guidance as to the study design, appropriate study population (including age), length of study, appropriate positive and negative controls, and study endpoints. (Please see two attachments to this consult for more specifics and background information.)                                                                                                                                                                                                                                                                                                                                                                                                            |         |                                       |                                                                                                                                                                      |                                            |
| SIGNATURE OF REQUESTOR<br><b>Marlene G. Swider</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |         |                                       | METHOD OF DELIVERY (Check one)<br><input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND |                                            |
| PRINTED NAME AND SIGNATURE OF RECEIVER                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |         |                                       | PRINTED NAME AND SIGNATURE OF DELIVERER                                                                                                                              |                                            |

## QT Review Team Consult

Re: NDA-22-181: sapropterin dihydrochloride (6R-BH4, Kuvan)

The Division of Gastroenterology Products requests a consultation from the QT review team for sapropterin (Kuvan, 6R-BH4; under NDA 22-181) regarding your recommendations for QT/cardiac safety evaluation of sapropterin. Sapropterin is a new molecular entity (NME) currently undergoing priority NDA review as a novel treatment for phenylketonuria (PKU). Sapropterin has been designated as an Orphan Drug.

NDA 22-181 is an electronic submission. The link to the original submission is:

\\Cdsub1\evsprod\NDA022181\0000

The link to the 120-day safety update, which contains a summary of the ECG/cardiac monitoring performed to date with sapropterin, is:

\\CDSESUB1\EVSPROD\NDA022181\022181.enx

### **Disease Background**

PKU is a rare, inborn error of metabolism (autosomal recessive) that results from the deficient activity of the enzyme phenylalanine hydroxylase. Patients with PKU have disordered metabolism of phenylalanine (Phe) that results in elevated blood Phe levels on exposure to Phe in the diet. The clinical manifestations of PKU are due to elevated blood Phe levels which are toxic. If left untreated, elevated blood Phe levels cause progressive neurocognitive impairment. Cardiac manifestations/pathology are not typically found in PKU. Currently available treatment for PKU is dietary restriction of Phe and supplementation with low-Phe medical foods, which is difficult to maintain throughout life. Compliance with therapy, particular in older children, adolescents, and adults, is extremely difficult. Thus, new treatments for PKU are needed.

### **Sapropterin Clinical Development Program**

Sapropterin is being proposed for the indication to “reduce blood phenylalanine (Phe) levels \_\_\_\_\_ in patients with hyperphenylalaninemia (HPA) due to Phenylketonuria (PKU).” \_\_\_\_\_  
\_\_\_\_\_

Sapropterin has been evaluated for safety and efficacy in approximately 580 patients with PKU, ages four years and older. Sapropterin was orally administered at doses of 5, 10, and 20 mg/kg/day once a day in clinical trials in support of the PKU indication. Exposure ranged from eight days (in approximately 440 patients) to up to 26 weeks (in approximately 80 patients). Important and pivotal clinical studies performed to date for the sapropterin PKU clinical development program are summarized in the following table:

Table 1: Table of Clinical Safety and Efficacy Studies: Sapropterin NDA 22-181

| Name                                             | Objectives                                       | Design & Control                                        | Regimen;                                                                                                                 | Patients, <sup>1</sup> n=                                                                  | Length of Treatment                  |
|--------------------------------------------------|--------------------------------------------------|---------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|--------------------------------------|
| PKU-001<br>Phase 1                               | Safety (S) and Efficacy (E); Identify responders | Open-Label (OL)                                         | 10 mg/kg/day                                                                                                             | 489 PKU patients                                                                           | 8 days                               |
| PKU-003<br>Phase 3                               | S and E; Reduced Phe                             | Randomized (R), Double-Blind (DB), Placebo Control (PC) | 10 mg/kg/day                                                                                                             | 88 (responders from PKU-001 study); 41 active (sapropterin), 47 placebo                    | 6 weeks                              |
| PKU-006<br>Phase 3                               | S and E; Dietary Phe tolerance                   | Part 1: OL<br>Part 2: R, DB, PC                         | 20 mg/kg/day                                                                                                             | Part 1: 90 PKU patients<br>Part 2: 46 (all responders from Part 1); 33 active, 12 placebo  | Part 1: 8 days<br>Part 2: 10 weeks   |
| PKU-004<br>Phase 3<br>Extension study to PKU-003 | S and E; dose ranging                            | OL                                                      | Part 1: 5→20→10 mg/kg/day (two weeks each dose followed by 10 mg/kg/day x four weeks)<br>Part 2: 5 or 10 or 20 mg/kg/day | 80 PKU patients (responders from PKU-001, subsequently treated in DB, R, PC study PKU-003) | Part 1: 10 weeks<br>Part 2: 12 weeks |

<sup>1</sup>Total unique patients = 579, 489 from PKU-001 (responders then treated in -003 and -004), and 90 from PKU-006 part 1 (responders then treated in Part 2)

In general, the results showed that sapropterin was found to reduce blood Phe levels in BH4-responsive PKU patients (approximately 20% of patients treated), and was found to have a favorable safety profile. Most Adverse Events (AEs) noted in clinical trials were mild, and were most commonly headache, vomiting and diarrhea. No cardiac findings were noted; however, **no routine ECG monitoring or evaluation was performed as part of the safety monitoring for the clinical studies conducted in PKU patients.**

The sponsor states that nonclinical hERG channel and cardiovascular safety studies with sapropterin showed the following:

- An hERG channel assay study (0162-06-005) was negative. The results of this study showed that the IC<sub>50</sub> for the effect of sapropterin on hERG potassium current was not determined, but was estimated to be >680 µM (terfenadine control was positive at 60 nM).
- An electrophysiologic/telemetry study (Study 0166-06-015) in eight conscious dogs at doses of 20, 50 or 100 mg/kg on Days 1, 4, 8 and 11 did not show abnormal findings by the cardiovascular parameters of ECG analysis, hemodynamic data (diastolic, systolic, and mean arterial pressures), inotropic state, and heart rate (NOEL 100 mg/kg).
- A second cardiovascular safety study (Study 0166-06-020) was performed in eight beagle dogs. Oral sapropterin (at doses up to 100 mg/kg) was administered in combination with sildenafil citrate. Results showed that sildenafil alone or in combination with sapropterin decreased diastolic pressure. No effect of sapropterin alone was noted on any of the cardiovascular parameters, but there

was an indication the sapropterin may attenuate or augment the observed sildenafil-induced increase in pulse pressure.

Sapropterin also underwent evaluation in single-dose or short-term PK and bioavailability studies. These studies are summarized as follows and in Table 2 below:

- P1501 was a Phase 1 study in healthy adults with single (N=6) and multiple dose (N=6) components. All patients received sapropterin. In patients treated with single dose on Day 1 and a second dose on Day 7, ECGs were performed at pre-dose, two hours after dose, and 24 hours after the Day 7 dose. In patients treated for seven days, ECGs were performed at pre-dose, two hours after each morning dose, and 24 hours after the final dose.
  - No abnormalities in ECG were observed.
  - No AEs were reported in the Cardiovascular System Organ Class.
- FB1602 was a Phase 1 multi-dose study in healthy adult males (N=6 sapropterin; N=2 placebo). Study subjects received their daily study drug treatment as three divided doses for seven days. ECGs were performed prior to each daily dose, and two hours after each daily dose, and 24 hours after the final dose.
  - No abnormalities in ECGs were observed.
  - No AEs were reported in the Cardiovascular System Organ Class.
- FB1701 was a Phase 1 multi-dose study in six healthy adult volunteers. Study subjects received their daily study drug treatment as three divided doses for seven days. ECGs were performed on Day 7 after completion of study. The study report does not clearly indicate if baseline ECGs were performed.
  - No abnormalities in ECGs were observed.
  - The study report does not provide or discuss objective ECG findings.

Table 2: Table of PK and Bioavailability Clinical Studies: Sapropterin NDA 22-181

| Name                                    | Objectives of Study                | Design & Control       | Regimen; Route                                                                   | Patients, n=                                    | Length of Treatment                                    |
|-----------------------------------------|------------------------------------|------------------------|----------------------------------------------------------------------------------|-------------------------------------------------|--------------------------------------------------------|
| PKU-005 <sup>1</sup>                    | PK fed v. fast juice v. H2O        | OL, R, Cross-over (CO) | 10 mg/kg, single dose, PO                                                        | 28 Healthy adults                               | 4 single doses, 7 days apart                           |
| PKU-009 <sup>1</sup>                    | PK Intact v. dissolved fed v. fast | OL, R, CO              | 10 mg/kg, single dose, PO                                                        | 44 Healthy adults                               | 3 single doses, 7 days apart                           |
| P1501 [PHN 111 PK SR; safety for P1501] | PK, S, and Metabolism              | OL, R                  | 100 or 200 mg PO (1.4—3.3 mg/kg/day); or 100 mg (4.2—4.9 mg/kg) PO, TID x 7 days | 12 Healthy adults [6 single dose; 6 multi-dose] | 2 single doses, 7 days apart, or Repeat doses x 7 days |
| FB1602                                  | PK, S                              | R, PC                  | 200 mg PO TID (10.1—11.2 mg/kg/d) x 7 days                                       | 8 Healthy adults [6 active; 2 placebo]          | 7 days                                                 |
| FB1701                                  | PK, S                              | OL                     | 200 mg PO, TID x 7 days (9.0—10.6 mg/kg/day)                                     | 6 Healthy adults                                | 7 days                                                 |

<sup>1</sup> Electrocardiograms (ECGs) not performed at Cmax

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
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Under this IND Study HTN-001, a Phase 2, randomized, double-blind, placebo-controlled, parallel-group study (N=39 placebo; N=77 sapropterin) was performed to evaluate the effects of sapropterin on blood pressure in patients with poorly controlled systemic hypertension. Sapropterin was administered as a 10 mg/kg/day dose, divided into two 5 mg/kg doses, for eight weeks. ECGs were performed at screening, prior to dosing at the Week 8 visit, and at the Week 12 visit (which was four weeks after the final dose).

The Sponsor reports that the mean values for ECG parameters, including QT interval, were similar between placebo and sapropterin-treated groups. Mean changes in ECGs from baseline were negligible in sapropterin-treated patients, and there were no adverse event reports that were suggestive of pro-arrhythmogenic effects of sapropterin.

### **Conclusion**

Sapropterin was found to reduce blood Phe levels in BH4-responsive PKU patients, and to have a generally favorable risk-benefit profile. Thus, the Division anticipates that sapropterin will likely receive approval for the treatment of PKU on or around November 28, 2007. However, no routine ECG or cardiac safety monitoring was performed during the clinical development program.

In the hypertension studies performed to date, patients were evaluated by ECG monitoring at doses up to 11 mg/kg, less than the proposed dosing for PKU of up to 20 mg/kg. A thorough QT study has not been performed as part of the clinical development program.

### **Questions**

1. Do you recommend that a thorough QT (TQT) or other cardiac safety study or evaluation be performed for sapropterin?
2. If yes, we anticipate that this study would be requested as a post-marketing commitment. Is the performance of a TQT (or other cardiac safety study or evaluation) as a post-marketing commitment reasonable or should a TQT or other evaluation be performed prior to approval?
3. If a TQT or other cardiac safety study/evaluation is recommended, please provide guidance as to the study design, appropriate study population (including age), length of study, appropriate positive and negative controls, and study endpoints.

### Highlights of Clinical Pharmacology

|                                           |                                                                                                              |                                                                                                                                             |
|-------------------------------------------|--------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Therapeutic dose                          | 5, 10, and 20 mg/kg/day                                                                                      |                                                                                                                                             |
| Maximum tolerated dose                    | Include if studied or NOAEL dose                                                                             |                                                                                                                                             |
| Principal adverse events                  | Upper respiratory tract infection, rhinorrhea , pharyngeal/laryngeal pain, diarrhea, abdominal pain, fatigue |                                                                                                                                             |
| Maximum dose tested                       | Single Dose                                                                                                  | 10/mg/kg                                                                                                                                    |
|                                           | Multiple Dose                                                                                                | No formal multiple dose PK study but Pop PK study was conducted                                                                             |
| Exposures Achieved at Maximum Tested Dose | Single Dose                                                                                                  | 121 ng/ml (27.8%) C <sub>max</sub><br>709 ng.hr/mL (31.1%) AUC                                                                              |
|                                           | Multiple Dose                                                                                                | N/A                                                                                                                                         |
| Range of linear PK                        | 5 – 20 mg/kg/day in Pop PK study                                                                             |                                                                                                                                             |
| Accumulation at steady state              | Assume no accumulation due to short half life (4hr)                                                          |                                                                                                                                             |
| Metabolites                               | Metabolites in human are not identified.                                                                     |                                                                                                                                             |
| Absorption                                | Absolute/Relative Bioavailability                                                                            | Not studied                                                                                                                                 |
|                                           | T <sub>max</sub>                                                                                             | • 4 hr (2 -6 hr)                                                                                                                            |
| Distribution                              | V <sub>d</sub> /F or V <sub>d</sub>                                                                          | 8350 L/70kg (SE: 16.9)                                                                                                                      |
|                                           | % bound                                                                                                      | Not known                                                                                                                                   |
| Elimination                               | Route                                                                                                        | Not known since a mass balance study has not been conducted.                                                                                |
|                                           | Terminal t <sub>1/2</sub>                                                                                    | • 4.68 hr ( CV:71.8%)                                                                                                                       |
|                                           | CL/F or CL                                                                                                   | 2100 L/hr/70kg (SE: 9.9)                                                                                                                    |
| Intrinsic Factors                         | Age                                                                                                          | Not significant                                                                                                                             |
|                                           | Sex                                                                                                          | Not significant                                                                                                                             |
|                                           | Race                                                                                                         | Not studied                                                                                                                                 |
|                                           | Hepatic & Renal Impairment                                                                                   | Not studied                                                                                                                                 |
| Extrinsic Factors                         | Drug interactions                                                                                            | Not studied                                                                                                                                 |
|                                           | Food Effects                                                                                                 | When the drug is dissolved in water under high fat meal, food effect was maximum:<br>C <sub>max</sub> 83% increase (90% CI 164.57 – 204.88) |

|                                          |                                                                                                |                                         |
|------------------------------------------|------------------------------------------------------------------------------------------------|-----------------------------------------|
|                                          |                                                                                                | AUC 86% increase (90% CII 70.07-204.81) |
| Expected High Clinical Exposure Scenario | 20 mg/kg/day as an intact tablet with high fat meal (food effect is 20% for an intact tablet). |                                         |

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/s/

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Marlene Swider  
10/12/2007 11:01:10 AM



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-181

BioMarin Pharmaceutical, Inc.  
Attention: Ms. Amy Waterhouse  
VP Regulatory & Government Affairs  
105 Digital Drive  
Novato, California 94949

Dear Ms. Waterhouse:

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

We are reviewing the Clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Please clarify the dates and treatments administered in the following datasets:

1. In the datasets DBLABS, DBLABSD, DBAE, DBAED, and DBAEGH in module 5.3.5.3.25.3.1 *Analysis Dataset*, please clarify the dates of performance of clinical laboratory tests [DBLABS and DBLABSD], and the dates of occurrence of adverse events [DBAE, DBAED, and DBAEGH].

For example, in the DBLABS dataset for patient 0004-0001 in column DOSEDT, the date entry is "16636". The date entry is not a recognizable date, and the "define.pdf" file and the corresponding appendices do not provide a way to readily interpret the date.

This comment also applies to the following:

- The DBLABS dataset columns: LABDT, DOSEDT1, DOSEDT4, DOSEDT6, and TREATED.
- The DBLABSD dataset columns: DOSEDT, LABDT, DOSEDT1, DOSEDT4, DOSEDT6, and TREATED.
- The DBAE dataset columns: STARTDAY, STOPDAY, and DOSEDT1.
- The DBAED dataset columns: DOSEDT1, STARTDAY, and STOPDAY.
- The DBAEGH dataset columns: STARTDAY, STOPDAY, DOSEDT1, DOSEDT3, DOSEDT4, and DOSEDT6.

Thus, from the information you have provided, we are unable to determine the dates of lab analyses, or the dates of adverse events (AEs).

2. In the datasets DBLABS, DBLABSD, DBAE, DBAED, and DBAEGH in module 5.3.5.3.25.3.1 *Analysis Dataset*, please clarify the treatments administered at the time of performance of clinical laboratory tests [DBLABS and DBLABSD], and at the time of occurrence of adverse events [DBAE, DBAED, and DBAEGH].

For example, in the DBAED dataset for patient D261-02-01, for the columns TRTCD (defined as “treatment group code”), TRTGRP (“treatment group”), TRTD (“treatment code for Daiichi subjects”), DOSED1 (“date of first dose on any study”), STARTDT (“adverse event start date”), and STOPDT (adverse event stop date), it is not clear to us whether the patient was receiving study drug when the AE “polyuria” occurred, during which phase of the study (controlled active or all active) the AE occurred, or the exposure to study drug at the time of the event. This information (from dataset DBAED) is summarized in the following table.

| USUBJID    | TRTCD | TRTGRP            | TRTD | DOSED1 | AE       | STARTDT | STOPDT |
|------------|-------|-------------------|------|--------|----------|---------|--------|
| D261-02-01 | 2     | CONTROLLED ACTIVE | S    | 9595   | POLYURIA | -       | -      |
| D261-02-01 | 2     | CONTROLLED ACTIVE | S    | 9595   | POLYURIA | -       | -      |
| D261-02-01 | 4     | ALL ACTIVE        | S    | 9595   | POLYURIA | -       | -      |
| D261-02-01 | 4     | ALL ACTIVE        | S    | 9595   | POLYURIA | -       | -      |

Thus, from the information you have provided, we are unable to determine the treatment the patient was being administered at the time of the AE.

3. Please clarify the following:
- Are the date entries as provided in the above noted datasets able to be converted to more recognizable dates that are amenable to data manipulation (i.e., would allow us to calculate, for example, length of time on study drug at the time of the event)?
  - Are the treatment-designation columns as provided in the above noted datasets able to be clarified such that the treatments administered at the time of the events are readily determined?
  - If dates and treatments administered cannot be easily converted or clarified, you will need to resubmit the datasets referenced above in a format that would allow us to easily recognize the dates and treatments administered, and to allow us to manipulate the data. For example, a more useful presentation for dates and treatments administered would be to use the same format used in the AAEDATA and ALABS datasets for the individual study report for Study PKU-003 found in module 5.3.5.1.25.3.1 *Analysis Datasets*. These revised datasets would need to be submitted as soon as possible.

If you have any questions, call Marlène Swider, Regulatory Project Manager, at (301) 796-2104.

Sincerely,

Julieann DuBeau, MSN, RN  
Chief, Project Management Staff (CPMS)  
Safety Regulatory Project Manager (SRPM)  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
CDER/FDA

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/s/

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Julieann DuBeau  
9/28/2007 05:04:29 PM

**NDA REGULATORY FILING REVIEW**  
**(Including Memo of Filing Meeting)**

NDA # 22-181

Supplement #

Efficacy Supplement Type SE-

Proprietary Name: Kuvan  
Established Name: sapropterin dihydrochloride  
Strengths: 100 mg

Applicant: BioMarin Pharmaceutical Inc.  
Agent for Applicant (if applicable):

Date of Application: May 25, 2007  
Date of Receipt: May 25, 2007  
Date clock started after UN:  
Date of Filing Meeting: July 13, 2007  
Filing Date: July 24, 2007  
Action Goal Date (optional):

User Fee Goal Date: November 25, 2007

Indication(s) requested: To reduce blood phenylalanine (Phe) levels \_\_\_\_\_ in patients  
with hyperphenylalaninemia due to Phenylketonuria (PKU). \_\_\_\_\_

Type of Original NDA: (b)(1) ☒ (b)(2) ☐  
AND (if applicable)  
Type of Supplement: (b)(1) ☐ (b)(2) ☐

**NOTE:**

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☐ P ☒  
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐  
Chemical Classification: (1,2,3 etc.) 1  
Other (orphan, OTC, etc.) orphan

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☐ Exempt (orphan, government) ☒  
Waived (e.g., small business, public health) ☐

**NOTE:** If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application.

*Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☐ NO ☒  
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒  
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐
- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐  
If no, explain:
- Was form 356h included with an authorized signature? YES ☒ NO ☐  
**If foreign applicant, both the applicant and the U.S. agent must sign.**
- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐  
If no, explain:
- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐
2. This application is an eNDA or combined paper + eNDA YES ☐  
This application is: All electronic ☐ Combined paper + eNDA ☐  
This application is in: NDA format ☐ CTD format ☐  
Combined NDA and CTD formats ☐

Does the eNDA, follow the guidance?

(<http://www.fda.gov/cder/guidance/2353fnl.pdf>)

YES ☐ NO ☐

**If an eNDA, all forms and certifications must be in paper and require a signature.**

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES ☒

**If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.**

Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☒
- Exclusivity requested? YES, 7 Years NO ☐  
*NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*
- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐  
**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**  
*NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."*
- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES ☒ NO ☐
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☐ NO ☐
- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐  
**(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)**  
*NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.*
- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☒ NO ☐
- PDUFA and Action Goal dates correct in tracking system? YES ☒ NO ☐  
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 69703
- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐  
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) December 28, 2004 NO ☐  
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) November 9, 2006 NO ☐  
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) \_\_\_\_\_ NO ☒  
If yes, distribute letter and/or relevant minutes before filing meeting.

### **Project Management**

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐  
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:  
Was the PI submitted in PLR format? YES ☒ NO ☐  
  
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☒ NO ☐
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☒ NO ☐
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?  
N/A ☐ YES ☐ NO ☐
- Risk Management Plan consulted to OSE/IO? N/A ☒ YES ☐ NO ☐
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☒ YES ☐ NO ☐

### **If Rx-to-OTC Switch or OTC application:**

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

### **Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES ☐ NO ☐

### **Chemistry**

- Did applicant request categorical exclusion for environmental assessment? YES ☐ NO ☐  
If no, did applicant submit a complete environmental assessment? YES ☒ NO ☐  
If EA submitted, consulted to EA officer, OPS? YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐
- If a parenteral product, consulted to Microbiology Team? YES ☐ NO ☐

ATTACHMENT

**MEMO OF FILING MEETING**

DATE: July 13, 2007

NDA #: 22-181

DRUG NAMES: Kuvan

APPLICANT: BioMarin Pharmaceuticals Inc.

BACKGROUND: Kuvan™ (sapropterin dihydrochloride) is a synthetic preparation of the dihydrochloride salt of naturally occurring tetrahydrobiopterin (6R-BH4 or BH4). It has the formal chemical name of (6R)-2-amino-6-[(1R,2S)-1,2-dihydroxypropyl]-5,6,7,8-tetrahydro-4(1H)-pteridinone dihydrochloride with a composition of C<sub>9</sub>H<sub>15</sub>N<sub>5</sub>O<sub>3</sub> · 2HCl and a molecular weight of 314.17. Kuvan™ is an immediate-release tablet formulation developed to reduce blood phenylalanine (Phe) levels \_\_\_\_\_ in patients with hyperphenylalaninemia (HPA) due to PKU. Kuvan™ increases the overall level of phenylalanine hydroxylase (PAH) activity by stimulating the residual enzyme activity of the altered PAH enzymes. \_\_\_\_\_

The proposed indication for Kuvan (sapropterin dihydrochloride) is to reduce blood Phe levels \_\_\_\_\_ in patients with HPA due to PKU. \_\_\_\_\_

ATTENDEES: Dr. Sushant Chakder, Dr. Anne Pariser, Dr. Ethan Hausman, Dr. Marie Kowblansky, Dr. Yichun Sun, Dr. Joyce Korvick, Dr. Hae Young Ahn, Dr. Mike Welch, Ryan Barraco

ASSIGNED REVIEWERS (including those not present at filing meeting) :

**Discipline/Organization**

Medical:

Secondary Medical:

Statistical:

Pharmacology:

Statistical Pharmacology:

Chemistry:

Environmental Assessment (if needed):

Biopharmaceutical:

Microbiology, sterility:

Microbiology, clinical (for antimicrobial products only):

DSI:

OPS:

**Reviewer**

Dr. Ethan Hausman

Dr. Stella Grosser

Dr. Fang Cai

Dr. Yichun Sun

Dr. Hae Young Ahn

Regulatory Project Management:  
Other Consults:

Ryan Barraco

Per reviewers, are all parts in English or English translation?  
If no, explain:

YES ☒ NO ☐

CLINICAL

FILE ☒

REFUSE TO FILE ☐

- Clinical site audit(s) needed?

YES ☒ NO ☐

If no, explain:

- Advisory Committee Meeting needed? YES, date if known \_\_\_\_\_ NO ☒

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY

N/A ☒

FILE ☐

REFUSE TO FILE ☐

STATISTICS

N/A ☐

FILE ☒

REFUSE TO FILE ☐

BIOPHARMACEUTICS

FILE ☒

REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed?  
YES

☐ NO ☒

PHARMACOLOGY/TOX

N/A ☐

FILE ☒

REFUSE TO FILE ☐

- GLP audit needed?

YES ☐ NO ☒

CHEMISTRY

FILE ☒

REFUSE TO FILE ☐

- Establishment(s) ready for inspection?

YES ☒ NO ☐

- Sterile product?

YES ☐ NO ☒

If yes, was microbiology consulted for validation of sterilization?

YES ☐ NO ☐

ELECTRONIC SUBMISSION:

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

☒ No filing issues have been identified.

☐ Filing issues to be communicated by Day 74. List (optional):

**ACTION ITEMS:**

1. ☐ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. ☐ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. ☐ Convey document filing issues/no filing issues to applicant by Day 74.

Ryan Barraco  
Regulatory Project Manager

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/s/

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Ryan Barraco  
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|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINISTRATION                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |         |                                                | <b>REQUEST FOR CONSULTATION</b>                                                                                                                                                                                          |                                             |
| TO (Division/Office):<br><b>CDER OSE CONSULTS</b><br><b>Attention: Cherye Milburn, OSE Regulatory Project Manager</b><br><b>WO22, RM 4323, HFD-430</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |         |                                                | FROM:<br><b>Ryan Barraco, Regulatory Project Manager</b><br><b>Division of Gastroenterology Products</b><br><b>WO22, RM 5109, HFD-180</b>                                                                                |                                             |
| DATE<br>8/17/07                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | IND NO. | NDA NO.<br>22-181                              | TYPE OF DOCUMENT<br>New NDA                                                                                                                                                                                              | DATE OF DOCUMENT<br>May 25, 2007            |
| NAME OF DRUG<br>Kuvan <sup>TM</sup> (sapropterin dihydrochloride) Tablets                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |         | PRIORITY CONSIDERATION<br>Priority Application | CLASSIFICATION OF DRUG<br>In-born Error in Metabolism                                                                                                                                                                    | DESIRED COMPLETION DATE<br>November 1, 2007 |
| NAME OF FIRM: BioMarin Pharmaceutical Inc.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |         |                                                |                                                                                                                                                                                                                          |                                             |
| <b>REASON FOR REQUEST</b><br><b>I. GENERAL</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |         |                                                |                                                                                                                                                                                                                          |                                             |
| <div style="display: flex; justify-content: space-between;"> <div style="width: 30%;"> <input type="checkbox"/> NEW PROTOCOL<br/> <input type="checkbox"/> PROGRESS REPORT<br/> <input type="checkbox"/> NEW CORRESPONDENCE<br/> <input type="checkbox"/> DRUG ADVERTISING<br/> <input type="checkbox"/> ADVERSE REACTION REPORT<br/> <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION<br/> <input type="checkbox"/> MEETING PLANNED BY         </div> <div style="width: 30%;"> <input type="checkbox"/> PRE-NDA MEETING<br/> <input type="checkbox"/> END OF PHASE II MEETING<br/> <input type="checkbox"/> RESUBMISSION<br/> <input type="checkbox"/> SAFETY/EFFICACY<br/> <input type="checkbox"/> PAPER NDA<br/> <input type="checkbox"/> CONTROL SUPPLEMENT         </div> <div style="width: 30%;"> <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER<br/> <input type="checkbox"/> FINAL PRINTED LABELING<br/> <input type="checkbox"/> LABELING REVISION<br/> <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE<br/> <input type="checkbox"/> FORMULATIVE REVIEW<br/> <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):         </div> </div> |         |                                                |                                                                                                                                                                                                                          |                                             |
| <b>II. BIOMETRICS</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |         |                                                |                                                                                                                                                                                                                          |                                             |
| STATISTICAL EVALUATION BRANCH<br><br><input type="checkbox"/> TYPE A OR B NDA REVIEW<br><input type="checkbox"/> END OF PHASE II MEETING<br><input type="checkbox"/> CONTROLLED STUDIES<br><input type="checkbox"/> PROTOCOL REVIEW<br><input type="checkbox"/> OTHER (SPECIFY BELOW):                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |         |                                                | STATISTICAL APPLICATION BRANCH<br><br><input type="checkbox"/> CHEMISTRY REVIEW<br><input type="checkbox"/> PHARMACOLOGY<br><input type="checkbox"/> BIOPHARMACEUTICS<br><input type="checkbox"/> OTHER (SPECIFY BELOW): |                                             |
| <b>III. BIOPHARMACEUTICS</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |         |                                                |                                                                                                                                                                                                                          |                                             |
| <input type="checkbox"/> DISSOLUTION<br><input type="checkbox"/> BIOAVAILABILITY STUDIES<br><input type="checkbox"/> PHASE IV STUDIES                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |         |                                                | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE<br><input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS<br><input type="checkbox"/> IN-VIVO WAIVER REQUEST                                                             |                                             |
| <b>IV. DRUG EXPERIENCE</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |         |                                                |                                                                                                                                                                                                                          |                                             |
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL<br><input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES<br><input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)<br><input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |         |                                                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY<br><input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE<br><input type="checkbox"/> POISON RISK ANALYSIS                                  |                                             |
| <b>V. SCIENTIFIC INVESTIGATIONS</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |         |                                                |                                                                                                                                                                                                                          |                                             |
| <input type="checkbox"/> CLINICAL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |         |                                                | <input type="checkbox"/> PRECLINICAL                                                                                                                                                                                     |                                             |
| <b>COMMENTS/SPECIAL INSTRUCTIONS:</b><br><br>The Division of Gastroenterology has received a new NDA, Kuvan <sup>TM</sup> (sapropterin dihydrochloride) Tablets. We respectfully request that DDMAC and DMETS review the package insert in PLR format, the carton label, and the immediate container label. The NDA is available electronically on the EDR and at the following link: <a href="#">\\CDSESUB1\EVSPROD\NDA022181\0000</a> . The PDUFA goal date is November 25, 2007. Please contact me if you have any questions.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |         |                                                |                                                                                                                                                                                                                          |                                             |
| SIGNATURE OF REQUESTER<br>Ryan Barraco, Regulatory Project Manager                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |         |                                                | METHOD OF DELIVERY (Check one)<br><input checked="" type="checkbox"/> DFS <span style="margin-left: 100px;"><input type="checkbox"/> HAND</span>                                                                         |                                             |

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/s/

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Ryan Barraco  
8/17/2007 03:42:15 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 22-181

Biomarin Pharmaceutical, Inc.  
Attention: Ben Dewees  
Senior Manager, Regulatory Affairs  
105 Digital Drive  
Novato, CA 94949

Dear Mr. Dewees:

Please refer to your May 25, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Kuvan<sup>TM</sup> (sapropterin dihydrochloride) Tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on July 24, 2007, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Ryan Barraco, Regulatory Project Manager, at (301) 796-0846.

Sincerely,

*{See appended electronic signature page}*

Julieann DuBeau, M.S.N., R.N.  
Chief, Project Management Staff  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Julieann DuBeau  
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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-181

**INFORMATION REQUEST LETTER**

Biomarin Pharmaceutical, Inc.  
Attention: Ben Dewees  
Senior Manager, Regulatory Affairs  
105 Digital Drive  
Novato, CA 94949

Dear Mr. Dewees:

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

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Please provide stability data for your drug product dissolved in water, orange juice, and apple juice at concentrations corresponding to the dose levels required. The testing conditions such as storage temperature and storage time need to be considered to reflect the conditions used by patients. The data should include testing at several time intervals over a three hour period and include 15, 30, and 60 minutes. Please demonstrate that the drug is completely dissolved in the liquids and volumes that are recommended in the package insert.

If you have any questions, call Ryan Barraco, Regulatory Project Manager, at (301) 796-0846.

Sincerely,

*{See appended electronic signature page}*

Julieann DuBeau, M.S.N., R.N.  
Chief, Project Management Staff  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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Julieann DuBeau  
7/16/2007 01:57:26 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-181

**NDA ACKNOWLEDGMENT**

Biomarin Pharmaceutical, Inc.  
Attention: Ben Dewees  
Senior Manager, Regulatory Affairs  
105 Digital Drive  
Novato, CA 94949

Dear Mr. Dewees:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

|                                 |                                     |
|---------------------------------|-------------------------------------|
| Name of Drug Product:           | sapropterin dihydrochloride Tablets |
| Review Priority Classification: | Priority (P)                        |
| Date of Application:            | May 25, 2007                        |
| Date of Receipt:                | May 25, 2007                        |
| Our Reference Number:           | NDA 22-181                          |

Please disregard the letter sent on June 18, 2007, which listed the incorrect user fee goal date of October 25, 2007. Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 24, 2007, in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be November 25, 2007.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have submitted pediatric studies with this application. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this application.

NDA 22-181

Page 2

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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

If you have any questions, call me at (301) 796-0846.

Sincerely,

*{See appended electronic signature page}*

Ryan Barraco  
Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Ryan Barraco  
6/28/2007 04:06:57 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-181

**NDA ACKNOWLEDGMENT**

Biomarin Pharmaceutical, Inc.  
Attention: Ben Dewees  
Senior Manager, Regulatory Affairs  
105 Digital Drive  
Novato, CA 94949

Dear Mr. Dewees:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

|                                 |                                     |
|---------------------------------|-------------------------------------|
| Name of Drug Product:           | sapropterin dihydrochloride Tablets |
| Review Priority Classification: | Priority (P)                        |
| Date of Application:            | May 25, 2007                        |
| Date of Receipt:                | May 25, 2007                        |
| Our Reference Number:           | NDA 22-181                          |

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 24, 2007, in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be October 25, 2007.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have submitted pediatric studies with this application. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this application.

NDA 22-181

Page 2

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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

If you have any questions, call me at (301) 796-0846.

Sincerely,

*{See appended electronic signature page}*

Ryan Barraco  
Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Ryan Barraco  
6/18/2007 12:25:30 PM

Executive CAC

Date of Meeting: November 9, 2004

Committee: Abigail Jacobs, Ph.D., HFD-024, Acting Chair  
Joseph Contrera, Ph.D., HFD-901, Member  
Barry Rosloff, Ph.D., HFD-120, Alternate Member  
Karen Davis-Bruno, Ph.D., Team Leader  
John Colerangle, DVM, Ph.D., Presenting Reviewer

Author of Draft: John Colerangle

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

IND #: 69,708

Drug Name: Phenoptin.

Sponsor: BioMarin Pharmaceuticals, Inc., 371 Bel Marin Keys Boulevard, Suite 210, Novato, CA 94949.

**Background:** The initial IND was submitted to the division on August 13, 2004. The submission contained a 4 week oral toxicity study conducted in F-344 rats and a 13-week oral toxicity study conducted in CD-1 mice to select doses for carcinogenicity studies. The dose selection studies were not reviewed by ECAC. The final study carcinogenicity reports were also included in the submission.

**Mouse Carcinogenicity Study:** In a 78-week carcinogenicity study, groups of male and female mice (60/sex/group) received sapropterin HCl by oral gavage at dose levels of 25, 80 and 250 mg/kg/day. The study duration does not meet the usual 104-Week study duration. Percentage survival was at least 48% for males and 58% for females in each group surviving for 78 weeks. The dose-related decrease in body weight observed in treated males (7-10%) relative to control was not associated with any concomitant decrease in food intake. In treated females, the lower food intake evident for all treated groups (7-8%) was associated with decrease (9-16%) in bodyweight. There were no treatment-related neoplastic findings.

**Rat Carcinogenicity Study:** In a 104-week carcinogenicity study, groups of male and female rats (60/sex/group) received sapropterin HCl by oral gavage at dose levels of 25, 80 and 250 mg/kg/day. There was a dose-related increase in incidence of benign adrenal pheochromocytoma in males. The incidence of benign adrenal pheochromocytoma was dose-related and significantly increased in HD males relative to the control group (by Fisher's Exact Probability test applied as a one-tailed test). The sponsor argued that the lower incidence of adrenal pheochromocytoma in the control group used in this study relative to the background data most likely accounts for the significant difference.

| SEX                     | MALES |      |      |       | FEMALES |      |      |      |
|-------------------------|-------|------|------|-------|---------|------|------|------|
|                         | 0     | 25   | 80   | 250   | 0       | 25   | 80   | 250  |
| Dose (mg/kg/d)          | 0     | 25   | 80   | 250   | 0       | 25   | 80   | 250  |
| # of animals examined   | 60    | 26   | 26   | 60    | 60      | 17   | 13   | 60   |
| Adrenal Medulla         |       |      |      |       |         |      |      |      |
| Benign Pheochromocytoma | 1/60  | 1/26 | 4/26 | 9/60* | 1/60    | 1/17 | 0/13 | 0/60 |

\* p<0.05

## **Executive CAC Recommendations and Conclusions:**

### **Rat:**

- There was no prior concurrence on selected doses, but the study was determined to be adequate.
- The Committee concludes that increased incidence of benign adrenal pheochromocytomas was drug related in males and noted that the incidence in the concurrent control was below the lowest incidence in the historical control range and that the high dose group was at the upper end of the reported historical control range.
- The Committee noted that the histopathology is incomplete because adrenal glands in more than half of the rats in the low and mid dose groups were not examined. When there is a finding, all dose groups should be examined.

### **Mouse:**

- The Committee noted that the mouse study was not ideal because it was only 78 weeks long, while the standard study is 2 years long. The committee accepted the study in view of the lack of tumor findings at 78 weeks and the lack of a strong tumor signal in the 104 week rat study.

Abigail Jacobs, Ph.D.  
Acting Chair, Executive CAC

cc:\n  
/Division File, HFD 510  
/KDavis-Bruno, Team Leader, HFD-510  
/JColerangle, Reviewer, HFD-510  
/PMadara, CSO/PM, HFD-510  
/ASeifried, HFD-024

**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**

/s/

Joe Contrera

11/15/04 02:03:12 PM

# ACTION PACKAGE CHECKLIST

| Application Information                                                                                                                                                                                                                                                                                                                                                                                                                                                |                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                      |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|
| BLA #<br>NDA # 22-181                                                                                                                                                                                                                                                                                                                                                                                                                                                  | BLA STN#<br>NDA Supplement # | If NDA, Efficacy Supplement Type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                      |
| Proprietary Name: Kuvan<br>Established Name: sapropterin dihydrochloride<br>Dosage Form: Tablets                                                                                                                                                                                                                                                                                                                                                                       |                              | Applicant: BioMarin Pharmaceutical, Inc.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                      |
| RPM: Cristi Stark                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                              | Division: 180                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Phone # 301-796-1007 |
| <b>NDAs:</b><br>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)<br>Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)<br><br>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) |                              | 505(b)(2) NDAs and 505(b)(2) NDA supplements:<br>Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):<br><br>Provide a brief explanation of how this product is different from the listed drug.<br><br><input type="checkbox"/> If no listed drug, check here and explain:<br><br><b>Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.</b><br><br><input type="checkbox"/> Confirmed <input type="checkbox"/> Corrected<br>Date: |                      |
| ❖ User Fee Goal Date                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                              | 11/25/07                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                      |
| ❖ Action Goal Date (if different)                                                                                                                                                                                                                                                                                                                                                                                                                                      |                              | 12/14/07                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                      |
| ❖ Actions                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                      |
| • Proposed action                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                              | <input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE<br><input type="checkbox"/> NA <input type="checkbox"/> CR                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                      |
| • Previous actions (specify type and date for each action taken)                                                                                                                                                                                                                                                                                                                                                                                                       |                              | X None                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                      |
| ❖ Advertising (approvals only)<br>Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (indicate dates of reviews)                                                                                                                                                                                                                                                                                                 |                              | <input checked="" type="checkbox"/> Requested in AP letter<br><input type="checkbox"/> Received and reviewed                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                      |

|                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                 |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ❖ Application Characteristics                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                 |
| Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority<br>Chemical classification (new NDAs only): Type 1                                                                                                                          |                                                                                                                                                                                                                                 |
| NDAs, BLAs and Supplements:<br><input checked="" type="checkbox"/> Fast Track<br><input type="checkbox"/> Rolling Review<br><input type="checkbox"/> CMA Pilot 1<br><input type="checkbox"/> CMA Pilot 2<br><br><input checked="" type="checkbox"/> Orphan drug designation |                                                                                                                                                                                                                                 |
| NDAs: Subpart H<br><input type="checkbox"/> Accelerated approval (21 CFR 314.510)<br><input type="checkbox"/> Restricted distribution (21 CFR 314.520)<br>Subpart I<br><input type="checkbox"/> Approval based on animal studies                                            | BLAs: Subpart E<br><input type="checkbox"/> Accelerated approval (21 CFR 601.41)<br><input type="checkbox"/> Restricted distribution (21 CFR 601.42)<br>Subpart H<br><input type="checkbox"/> Approval based on animal studies  |
| NDAs and NDA Supplements:<br><input type="checkbox"/> OTC drug<br><br>Other:                                                                                                                                                                                                |                                                                                                                                                                                                                                 |
| Other comments:                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                 |
| ❖ Application Integrity Policy (AIP)                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                 |
| • Applicant is on the AIP                                                                                                                                                                                                                                                   | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No                                                                                                                                                             |
| • This application is on the AIP                                                                                                                                                                                                                                            | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No                                                                                                                                                             |
| • Exception for review ( <i>file Center Director's memo in Administrative Documents section</i> )                                                                                                                                                                           | <input type="checkbox"/> Yes <input type="checkbox"/> No                                                                                                                                                                        |
| • OC clearance for approval ( <i>file communication in Administrative Documents section</i> )                                                                                                                                                                               | <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action                                                                                                                                                          |
| ❖ Public communications (approvals only)                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                 |
| • Office of Executive Programs (OEP) liaison has been notified of action                                                                                                                                                                                                    | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No                                                                                                                                                             |
| • Press Office notified of action                                                                                                                                                                                                                                           | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No                                                                                                                                                             |
| • Indicate what types (if any) of information dissemination are anticipated                                                                                                                                                                                                 | <input type="checkbox"/> None<br><input checked="" type="checkbox"/> FDA Press Release<br><input checked="" type="checkbox"/> FDA Talk Paper<br><input checked="" type="checkbox"/> CDER Q&As<br><input type="checkbox"/> Other |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>❖ <b>Exclusivity</b></p> <ul style="list-style-type: none"> <li>NDAs: Exclusivity Summary (approvals only) (<i>file Summary in Administrative Documents section</i>)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <p><input checked="" type="checkbox"/> Included</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?           <ul style="list-style-type: none"> <li>NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> <li>NDAs: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> <li>NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> <li>NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul> </li> </ul> | <p><input checked="" type="checkbox"/> No    <input type="checkbox"/> Yes</p> <p><input checked="" type="checkbox"/> No    <input type="checkbox"/> Yes<br/>If, yes, NDA/BLA #                      and date exclusivity expires:</p> <p><input type="checkbox"/> No    <input type="checkbox"/> Yes<br/>If, yes, NDA #                      and date exclusivity expires:</p> <p><input type="checkbox"/> No    <input type="checkbox"/> Yes<br/>If, yes, NDA #                      and date exclusivity expires:</p> <p><input type="checkbox"/> No    <input type="checkbox"/> Yes<br/>If, yes, NDA #                      and date exclusivity expires:</p> |
| <p>❖ <b>Patent Information (NDAs and NDA supplements only)</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <ul style="list-style-type: none"> <li><b>Patent Information:</b><br/>Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <p><input checked="" type="checkbox"/> Verified<br/><input type="checkbox"/> Not applicable because drug is an old antibiotic.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <ul style="list-style-type: none"> <li><b>Patent Certification [505(b)(2) applications]:</b><br/>Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | <p>21 CFR 314.50(i)(1)(i)(A)<br/><input type="checkbox"/> Verified</p> <p>21 CFR 314.50(i)(1)<br/><input type="checkbox"/> (ii)    <input type="checkbox"/> (iii)</p> <p><input type="checkbox"/> No paragraph III certification<br/>Date patent will expire</p>                                                                                                                                                                                                                                                                                                                                                                                                 |
| <ul style="list-style-type: none"> <li>[505(b)(2) applications] For each <b>paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i></li> <li>[505(b)(2) applications] For each <b>paragraph IV</b> certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.</li> </ul> <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's</p>                                                                                                                                                                                                                                                                                                                                        | <p><input type="checkbox"/> N/A (no paragraph IV certification)<br/><input type="checkbox"/> Verified</p> <p><input type="checkbox"/> Yes    <input type="checkbox"/> No</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

☐ Yes ☐ No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

☐ Yes ☐ No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                           |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| <p>within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p> |                                                                           |
| <b>Summary Reviews</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                           |
| ❖ Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Off Dir-12/13/07, P/T Off 12/4/07, Chem Dir – 11/21/07, Clin TL – 12/3/07 |
| ❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                           |
| <b>Labeling</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                           |
| ❖ Package Insert                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                           |
| <ul style="list-style-type: none"> <li>Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                          |                                                                           |
| <ul style="list-style-type: none"> <li>Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                    | 11/21/07                                                                  |
| <ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 5/25/07                                                                   |
| <ul style="list-style-type: none"> <li>Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                             | N/A                                                                       |
| ❖ Patient Package Insert                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                           |
| <ul style="list-style-type: none"> <li>Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                          |                                                                           |
| <ul style="list-style-type: none"> <li>Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                    | 11/21/07                                                                  |
| <ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 5/25/07                                                                   |
| <ul style="list-style-type: none"> <li>Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                             | N/A                                                                       |
| ❖ Medication Guide                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                           |
| <ul style="list-style-type: none"> <li>Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                          |                                                                           |
| <ul style="list-style-type: none"> <li>Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                    |                                                                           |
| <ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                           |
| <ul style="list-style-type: none"> <li>Other relevant labeling (e.g., most recent 3 in class, class labeling)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                           |
| ❖ Labels (full color carton and immediate-container labels)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                           |
| <ul style="list-style-type: none"> <li>Most-recent division-proposed labels (only if generated after latest applicant submission)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                           |
| <ul style="list-style-type: none"> <li>Most recent applicant-proposed labeling</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 11/21/07                                                                  |

|                                                                                                           |                                                                                                                                                                                                                                                |
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| ❖ Labeling reviews and minutes of any labeling meetings ( <i>indicate dates of reviews and meetings</i> ) | <input checked="" type="checkbox"/> DMETS<br><input type="checkbox"/> DSRCS<br><input checked="" type="checkbox"/> DDMAC<br><input type="checkbox"/> SEALD<br><input type="checkbox"/> Other reviews<br><input type="checkbox"/> Memos of Mtgs |
|-----------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

| Administrative Documents                                                                                                                                                                                                              |                                                          |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|
| ❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) ( <i>indicate date of each review</i> )                                                                                                                     | RPM - 8/21/07, Chem - 7/9/07                             |
| ❖ NDA and NDA supplement approvals only: Exclusivity Summary ( <i>signed by Division Director</i> )                                                                                                                                   | X Included                                               |
| ❖ AIP-related documents <ul style="list-style-type: none"> <li>Center Director's Exception for Review memo</li> <li>If AP: OC clearance for approval</li> </ul>                                                                       | N/A                                                      |
| ❖ Pediatric Page (all actions)                                                                                                                                                                                                        | X Included                                               |
| ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. ( <i>Include certification.</i> ) | X Verified, statement is acceptable                      |
| ❖ Postmarketing Commitment Studies                                                                                                                                                                                                    | <input type="checkbox"/> None                            |
| <ul style="list-style-type: none"> <li>Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>)</li> </ul>                                                                | 10/23/07, 11/9/07, 11/29/07, 12/6/07, 12/7/07, 12/10/07  |
| <ul style="list-style-type: none"> <li>Incoming submission documenting commitment</li> </ul>                                                                                                                                          | 11/27/07                                                 |
| ❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)                                                                                                                                        | 9/28/07, 9/27/07, 8/7/07, 7/16/07, 6/28/07, 6/18/07      |
| ❖ Internal memoranda, telecons, email, etc.                                                                                                                                                                                           | 10/25/07, 10/25/07, 12/7/07                              |
| ❖ Minutes of Meetings                                                                                                                                                                                                                 |                                                          |
| <ul style="list-style-type: none"> <li>Pre-Approval Safety Conference (<i>indicate date; approvals only</i>)</li> </ul>                                                                                                               | 11/29/07                                                 |
| <ul style="list-style-type: none"> <li>Pre-NDA/BLA meeting (<i>indicate date</i>)</li> </ul>                                                                                                                                          | <input type="checkbox"/> No mtg 10/12/06                 |
| <ul style="list-style-type: none"> <li>EOP2 meeting (<i>indicate date</i>)</li> </ul>                                                                                                                                                 | <input type="checkbox"/> No mtg 11/22/04                 |
| <ul style="list-style-type: none"> <li>Other (e.g., EOP2a, CMC pilot programs)</li> </ul>                                                                                                                                             | N/A                                                      |
| ❖ Advisory Committee Meeting                                                                                                                                                                                                          | X No AC meeting                                          |
| <ul style="list-style-type: none"> <li>Date of Meeting</li> </ul>                                                                                                                                                                     |                                                          |
| <ul style="list-style-type: none"> <li>48-hour alert or minutes, if available</li> </ul>                                                                                                                                              |                                                          |
| ❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)                                                                                                                                                           | N/A                                                      |
| CMC/Product Quality Information                                                                                                                                                                                                       |                                                          |
| ❖ CMC/Product review(s) ( <i>indicate date for each review</i> )                                                                                                                                                                      | 11/19/07, 11/21/07                                       |
| ❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer ( <i>indicate date for each review</i> )                                                                                                           | X None                                                   |
| ❖ BLAs: Product subject to lot release (APs only)                                                                                                                                                                                     | <input type="checkbox"/> Yes <input type="checkbox"/> No |
| ❖ Environmental Assessment (check one) (original and supplemental applications)                                                                                                                                                       |                                                          |
| <ul style="list-style-type: none"> <li>X Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)</li> </ul>                     | Refer to CMC review - acceptable                         |
| <ul style="list-style-type: none"> <li><input type="checkbox"/> Review &amp; FONSI (<i>indicate date of review</i>)</li> </ul>                                                                                                        |                                                          |
| <ul style="list-style-type: none"> <li><input type="checkbox"/> Review &amp; Environmental Impact Statement (<i>indicate date of each review</i>)</li> </ul>                                                                          |                                                          |

|                                                                                         |                                                                                              |
|-----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|
| ❖ NDAs: Microbiology reviews (sterility & apyrogenicity) (indicate date of each review) | X Not a parenteral product                                                                   |
| ❖ Facilities Review/Inspection                                                          |                                                                                              |
| ❖ NDAs: Facilities inspections (include EER printout)                                   | Date completed: 11/21/07<br>X Acceptable<br><input type="checkbox"/> Withhold recommendation |

|                                                                                                                                                                                                                                                                                      |                                                                                                                                        |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| ❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> <li>Facility review (indicate date(s))</li> <li>Compliance Status Check (approvals only, both original and supplemental applications) (indicate date completed, must be within 60 days prior to AP)</li> </ul> | <input type="checkbox"/> Requested<br><input type="checkbox"/> Accepted<br><input type="checkbox"/> Hold                               |
| ❖ NDAs: Methods Validation                                                                                                                                                                                                                                                           | <input type="checkbox"/> Completed<br><input type="checkbox"/> Requested<br><input type="checkbox"/> Not yet requested<br>X Not needed |

## Nonclinical Information

|                                                                                                              |                                                      |
|--------------------------------------------------------------------------------------------------------------|------------------------------------------------------|
| ❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)                      | 11/27/07, 12/4/07                                    |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review) | X None                                               |
| ❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)                           | <input type="checkbox"/> No carc refer to P/T review |
| ❖ ECAC/CAC report/memo of meeting                                                                            | 11/15/04                                             |
| ❖ Nonclinical inspection review Summary (DSI)                                                                | X None requested                                     |

## Clinical Information

|                                                                                                                        |                                                     |
|------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|
| ❖ Clinical review(s) (indicate date for each review)                                                                   | ongoing                                             |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review                                      | Refer to clinical review                            |
| ❖ Clinical consult reviews from other review disciplines/divisions/Centers (indicate date of each review)              | <input type="checkbox"/> None 11/7/07               |
| ❖ Microbiology (efficacy) reviews(s) (indicate date of each review)                                                    | X Not needed                                        |
| ❖ Safety Update review(s) (indicate location/date if incorporated into another review)                                 | Refer to clinical review                            |
| ❖ Risk Management Plan review(s) (including those by OSE) (indicate location/date if incorporated into another review) | N/A                                                 |
| ❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date of each review)                | X Not needed                                        |
| ❖ DSI Inspection Review Summary(ies) (include copies of DSI letters to investigators)                                  | <input type="checkbox"/> None requested             |
| • Clinical Studies                                                                                                     | 11/15/07                                            |
| • Bioequivalence Studies                                                                                               | N/A                                                 |
| • Clin Pharm Studies                                                                                                   | N/A                                                 |
| ❖ Statistical Review(s) (indicate date for each review)                                                                | <input type="checkbox"/> None 12/13/07              |
| ❖ Clinical Pharmacology review(s) (indicate date for each review)                                                      | <input type="checkbox"/> None 10/29/07,<br>11/27/07 |

## Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) Or it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) Or it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) And no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) And all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) Or the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) Or the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**ADMINISTRATIVE REVIEW OF NDA ACTION PACKAGE  
OFFICE OF DRUG EVALUATION III**

**NDA:** 22-181

**Drug:** Kuvan (sapropterin dihydrochloride) Tablets

**Classification:** 1P; 505(b) (1)

**Sponsor:** BioMarin Pharmaceuticals, Inc.

**Project Manager/CSO:** Cristi Stark

**Indication:** 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.

**Reviewer:** Maria Walsh

**Received:** 11/30/07

**Review Completed:** 12/4/07

**Review Cycle 1**

**Date Submitted:** 5/25/07

**Date Received:** 5/25/07

**Goal Date:** 11/25/07 (Action date: 12/13/07)

**Extended Goal Date:** N/A

**Proposed Action:** AP

|                                | STATUS    | COMMENTS                                                     |
|--------------------------------|-----------|--------------------------------------------------------------|
| <b>ACTION LETTER</b>           | Draft     | Awaiting PerRC assessment of WR and pediatric PMCs.          |
| <b>PUBLIC COMMUNICATIONS</b>   | Pending   | Awaiting Press Release, Talk Paper, Q&As.                    |
| <b>PATENT INFORMATION</b>      | Completed | Submission of Form FDA 3542a was verified.                   |
| <b>SUMMARY REVIEWS</b>         |           |                                                              |
| <b>DIVISION SUMMARY REVIEW</b> | Pending   |                                                              |
| <b>LARM</b>                    | N/A       |                                                              |
| <b>LABELING</b>                |           |                                                              |
| • PI                           | Completed | Final SPL submitted 11/21/07                                 |
| • PPI                          | Completed | Final SPL submitted 11/21/07                                 |
| • Med Guide                    | N/A       |                                                              |
| • Labels                       | Completed | Draft labels submitted 11/21/07; FPL requested in AP letter. |

|                                             |           |                                                                                                                                           |
|---------------------------------------------|-----------|-------------------------------------------------------------------------------------------------------------------------------------------|
| • <b>DMETS REVIEW</b>                       | Completed | 11/14/07. Recommendations to remove circular graphic and decrease prominence of net quantity not seen in draft labels submitted 11/21/07. |
| • <b>DSRCS REVIEW</b>                       | N/A       |                                                                                                                                           |
| • <b>DDMAC REVIEW</b>                       | Completed | 11/15/07.                                                                                                                                 |
| • <b>SEALD REVIEW</b>                       | Pending   |                                                                                                                                           |
| <b>ADMINISTRATIVE DOCUMENTS</b>             |           |                                                                                                                                           |
| <b>ADMIN REVIEWS</b>                        | Completed | RPM Filing Review 8/21/07                                                                                                                 |
| <b>EXCLUSIVITY CHECKLIST</b>                | Draft     | Sponsor requested 7-years Orphan Drug exclusivity.                                                                                        |
| <b>AIP DOCUMENTS</b>                        | N/A       |                                                                                                                                           |
| <b>PEDIATRIC PAGE</b>                       | Completed | 11/26/07. PREA does not apply - orphan indication.                                                                                        |
| <b>DEBARMENT STATEMENT</b>                  | Completed | Copy of debarment certification in action package.                                                                                        |
| <b>POSTMARKETING COMMITMENTS</b>            | Pending   | Awaiting submission of sponsor's commitment.                                                                                              |
| <b>OUTGOING CORRESPONDENCE</b>              | Completed |                                                                                                                                           |
| <b>INTERNAL MEMOS/TELECONS /EMAIL</b>       | Pending   |                                                                                                                                           |
| <b>MINUTES OF MEETINGS</b>                  | Completed | EOP2 11/22/04; Pre-NDA 10/12/06.                                                                                                          |
| <b>ADVISORY COMMITTEE MEETING DOCUMENTS</b> | N/A       |                                                                                                                                           |
| <b>FR NOTICES</b>                           | N/A       |                                                                                                                                           |
| <b>CMC/PRODUCT QUALITY INFORMATION</b>      |           |                                                                                                                                           |
| <b>CMC/PRODUCT REVIEWS</b>                  | Completed | 11/19/07; 11/21/07                                                                                                                        |
| <b>ENVIRONMENTAL ASSESSMENT</b>             | Completed | Categorical Exclusion granted (CMC review 11/19/07)                                                                                       |
| <b>FACILITY INSPECTIONS</b>                 | Completed | Acceptable recommendation (EER Summary Report 11/21/07)                                                                                   |
| <b>METHODS VALIDATION</b>                   | Pending   | No box is checked. CMC review indicates that a MV package was not reviewed.                                                               |

| NONCLINICAL INFORMATION             |           |                                      |
|-------------------------------------|-----------|--------------------------------------|
| PHARM/TOX                           | Completed | 11/27/07                             |
| STATS REVIEW OF CARCI STUDIES       | N/A       |                                      |
| ECAC/CAC REPORT                     | Completed | Minutes 11/15/04.                    |
| NONCLINICAL INSPECTION REVIEW (DSI) | N/A       |                                      |
| CLINICAL INFORMATION                |           |                                      |
| CLINICAL REVIEW                     | Draft     |                                      |
| FINANCIAL DISCLOSURE                | Pending   |                                      |
| MICROBIOLOGY                        | N/A       |                                      |
| SAFETY UPDATE                       | Pending   | SU submitted 9/21/07.                |
| RISK MANAGEMENT PLAN                | N/A       |                                      |
| CONTROLLED SUBSTANCE STAFF REVIEW   | N/A       |                                      |
| CLINICAL INSPECTION REVIEW (DSI)    | Completed | 11/15/07. Acceptable recommendation. |
| STATISTICAL                         | Pending   |                                      |
| CLIN PHARM                          | Completed | 10/29/07; 11/27/07                   |

**PHARM/TOX OFFICE REVIEW:** Action Package to Abby Jacobs on 12/3/07. Tertiary review memo 12/4/07.

**PRODUCT QUALITY OFFICE REVIEW:** Action Package to Elaine Morefield on 12/4/07. Tertiary review memo 11/21/07.

**Comments:**

1. Indicate N/A in the box for FR Notices under Administrative Documents.
2. Check the appropriate box for Methods Validation.
3. For future action packages:
  - Omit a tab in the action package for any item marked N/A on the Action Package Checklist.
  - Place tabs/documents in the order they appear on the Action Package Checklist (e.g. Product Quality reviews

and Pharm/Tox reviews should follow Administrative Documents; Exclusivity Summary, Debarment Certification, and Pediatric Page should be placed with the Administrative Documents).