

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205065Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # NDA 205065

SUPPL #

HFD # 180

Trade Name Kuvan

Generic Name Sapropterin dihydrochloride

Applicant Name BioMarin

Approval Date, If Known

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.

No clinical studies were conducted for this NDA and the company requested a biowaiver for the conducting BA/BE studies. Based on the information submitted for the composition, solubility, and osmolarity of Kuvan (sapropterin dihydrochloride) Powder for Oral Solution, the waiver for in-vivo bioavailability/bioequivalence studies was granted.

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?

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# 022181

Sapropterin dihydrochloride

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

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

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"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

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 #1 !
IND # YES ! NO
! Explain:

Investigation #2 !
IND # YES ! NO
! Explain:

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

JESSICA M BENJAMIN
12/17/2013

ANDREW E MULBERG
12/17/2013

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 205065 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Kuvan Established/Proper Name: sapropterin dihydrochloride Dosage Form: powder for oral solution		Applicant: BioMarin Agent for Applicant (if applicable):
RPM: Jessica Benjamin		Division: DGIEP
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(For additional information regarding 505(b)(2)s, please refer to http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/RegulatoryAffairsTeam/ucm027499.htm)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>12/6/13</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics ³</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Breakthrough Therapy designation </p> <p> <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and 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> 	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes If, yes, NDA/BLA # 022181 and date exclusivity expires: 12/13/14
<ul style="list-style-type: none"> (b)(2) NDAs only: 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> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: 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> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: 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> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: 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. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: 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. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III 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). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV 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> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(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 the rest of the patent questions.

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).

<p>(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?</p> <p>(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 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 OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) Approval 12/19/13
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	12/18/13
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	2/8/13
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	n/a

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	12/18/13 (see label under most recent PI tab)
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	n/a
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	n/a
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	10/21/13
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	7/9/13 7/9/13
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 6/4/13 <input checked="" type="checkbox"/> DMEPA 10/24/13 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 12/10/13 <input checked="" type="checkbox"/> OPDP (DDMAC) 12/10/13 <input checked="" type="checkbox"/> SEALD 12/17/13 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	4/17/13
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input checked="" type="checkbox"/> Not a (b)(2) <input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>orphan designation</u> • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ 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>) 	<input checked="" type="checkbox"/> Verified, statement is acceptable

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Outgoing communications (<i>letters, including response to FD RR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	11/15/13; 11/6/13; 7/12/13; 6/10/13; 6/6/13; 4/22/13; 2/13/13
❖ Internal memoranda, telecons, etc.	n/a
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• EOP2 meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	Type C CMC – 6/21/12
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12/18/13
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 11/22/13
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	11/5/13
• Clinical review(s) (<i>indicate date for each review</i>)	n/a
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Clinical review dated 11/5/13 states no new clinical information as submitted with this NDA
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None PMHS 11/25/13
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management	
• REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)	
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested

⁶ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Biostatistics <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 10/25/13; 4/4/12
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 12/2/13; 10/28/13; 3/28/13
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 11/22/13; 10/9/13; 4/9/13
❖ Microbiology Reviews	<input checked="" type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input type="checkbox"/> None Biopharmaceutics 10/8/13; 3/14/13

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	Pg 37 of CMC review dated 10/9/13
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷</i>)	Date completed: <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

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/s/

JESSICA M BENJAMIN
12/20/2013



NDA 205065

LABELING PMR/PMC DISCUSSION COMMENTS

BioMarin Pharmaceutical Inc.
Attention: Manisha S. Deshmukh, MPharm, MS
Associate Director, Regulatory Affairs
105 Digital Drive
Novato, CA 94949

Dear Ms. Deshmukh:

Please refer to your February 8, 2013 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Kuvan (sapropterin dihydrochloride) Powder for Oral Solution, 100 mg.

We also refer to our April 22, 2013, letter in which we notified you of our target date of November 15, 2013 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012.”

On September 5, 2013, we received your September 5, 2013 proposed labeling submission to this application, and have proposed revisions that are included as an enclosure. These revisions have been reviewed and cleared to the level of Cross Discipline Team Leader.

If you have any questions, call me, at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Jessica M. Benjamin, M.P.H.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE: Package Insert

23 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JESSICA M BENJAMIN
11/15/2013

From: [Benjamin, Jessica](#)
To: [Manisha Deshmukh](#)
Cc: [Benjamin, Jessica](#)
Subject: NDA 205065 - container label comment
Date: Wednesday, November 06, 2013 11:07:17 AM

Hi Manisha,

Please refer to NDA 205065 and your submission dated October 21, 2013. We have the following comment for the container label:

Please update the equivalency statement to read ***100 mg sapropterin dihydrochloride equivalent to 76.8 mg of sapropterin**

Let me know if you have any questions.

Regards,
Jessica

Jessica M. Benjamin, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of New Drugs III
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9904 *fax*

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/s/

JESSICA M BENJAMIN
11/06/2013



NDA 205065

INFORMATION REQUEST

BioMarin Pharmaceutical Inc.
Attention: Manisha S. Deshmukh, MPharm., MS
Associate Director, Regulatory Affairs
105 Digital Drive
Novato, CA 94949

Dear Ms. Deshmukh:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Kuvan (sapropterin dihydrochloride) Powder for Oral Solution.

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 data to support the following your claims in *Section 2.2 Introduction Administration* of the Application:

[Redacted content] (b) (4)

Please provide this information by Monday, July 22, 2013. If you have any questions, call Cathy Tran-Zwanetz, Regulatory Project Manager, at (301) 796-3877.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Branch Chief, Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

MOO JHONG RHEE
07/12/2013
Chief, Branch IV



NDA 205065

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

BioMarin Pharmaceutical Inc.
105 Digital Drive
Novato, CA 94949

ATTENTION: Manisha S. Deshmukh, MPharm., MS
Associate Director, Regulatory Affairs

Dear Ms. Deshmukh:

Please refer to your New Drug Application (NDA) dated February 7, 2013, received February 8, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Sapropterin Dihydrochloride Powder for Oral Solution, 100 mg.

We also refer to your April 10, 2013, correspondence, received April 11, 2013, requesting review of your proposed proprietary name, Kuvan. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Kuvan will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your April 10, 2013 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Phong Do, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4795. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Jessica Benjamin at (301) 796-3924

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
07/09/2013

From: [Benjamin, Jessica](#)
To: [Manisha Deshmukh](#)
Cc: [Benjamin, Jessica](#)
Subject: NDA 205065 - Request for Information
Date: Monday, June 10, 2013 12:42:23 PM

Dear Manisha:

Please refer to NDA 205065 for Kuvan Powder for Oral Solution. As part of our on-going review of this application, we have the following information request:

Propose an established pharmacologic class (EPC) to be included in the Highlights section, and provide a rationale for your proposal. The EPC should be scientifically valid and clinically meaningful (see FDA guidance, “Labeling for Human Prescription Drug and Biological Products — Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information”).

We appreciate a prompt response to our request. Let me know if you have any questions.

Regards,
Jessica

Jessica M. Benjamin, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of New Drugs III
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9904 *fax*

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/s/

JESSICA M BENJAMIN
06/10/2013



NDA 205065

INFORMATION REQUEST

BioMarin Pharmaceutical Inc.
Attention: Manisha S. Deshmukh, MPharm., MS
Associate Director, Regulatory Affairs
105 Digital Drive
Novato, CA 94949

Dear Ms. Deshmukh:

Please refer to your New Drug Application (NDA) dated February 7, 2013, received February 8, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Kuvan (sapropterin dihydrochloride) Powder for Oral Solution, 100 mg.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. Highlights (HL) must be limited in length to a half page and should be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font. The HL section of your labeling is greater than half a page and the margins should be adjusted to ½ inch.
2. White space must be present before each major heading in HL. White space should be added between the “Recent Major Changes” section and “Indications and Usage” section in HL.
3. Recent Major Changes in HL must include headings in addition to subheadings for labeling sections affected by the recent major change. For example, “Dosage and Administration, Administration (2.2) --- 11/2013”.
4. When clinical trials adverse reactions data is included in the full prescribing information (FPI), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

5. When postmarketing adverse reaction data is included in the FPI, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

6. FDA-approved patient labeling (e.g., Patient Information) must not be included as a subsection under Section 17 (Patient Counseling Information) of the full prescribing information (FPI) and instead the patient labeling may immediately follow Section 17.
7. Section 17 (Patient Counseling Information) of the FPI must use the following statement at the beginning of Section 17:

“See FDA-approved patient labeling (Patient Information)”

We request that you resubmit labeling that addresses these issues by June 24, 2013. The resubmitted labeling will be used for further labeling discussions.

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

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

RICHARD W ISHIHARA
06/06/2013



NDA 205065

FILING COMMUNICATION

BioMarin Pharmaceutical Inc.
Attention: Manisha S. Deshmukh, MPharm., MS
Associate Director, Regulatory Affairs
105 Digital Drive
Novato, CA 94949

Dear Ms. Deshmukh:

Please refer to your New Drug Application (NDA) dated February 7, 2013, received February 8, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Kuvan (sapropterin dihydrochloride) Powder for Oral Solution, 100 mg.

We also refer to your amendments dated March 22 and 29, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is December 8, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by November 15, 2013.

We request that you submit the following information:

1. Complete dissolution data for Kuvan (sapropterin dihydrochloride) Powder for Oral Solution, which include the individual data, mean, % CV, dates of dissolution testing, and dissolution profiles.

2. Dissolution method validation report for the Kuvan powder drug product.
3. You have submitted only three months of stability data, which is insufficient for expiration dating your product. We will accept additional stability data while the product is under review using the submission schedule you propose in the submission: stability results through nine months of storage under long-term conditions and six months of storage under accelerated conditions can be submitted during the first 3-months of application review.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, the proposed package insert (PI), and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

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

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

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

Sincerely,

{See appended electronic signature page}

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

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/s/

ANDREW E MULBERG
04/22/2013



NDA 205065

NDA ACKNOWLEDGMENT

BioMarin Pharmaceutical Inc.
Attention: Manisha S. Deshmukh, MPharm., MS
Associate Director, Regulatory Affairs
105 Digital Drive
Novato, CA 94949

Dear Ms. Deshmukh:

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

Name of Drug Product: Kuvan (sapropterin dihydrochloride) Powder for Oral Solution,
100 mg

Date of Application: February 7, 2013

Date of Receipt: February 8, 2013

Our Reference Number: NDA 205065

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 April 9, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The NDA number provided above should be cited 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 and Inborn Errors Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Jessica M. Benjamin, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

JESSICA M BENJAMIN
02/13/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 22181

MEETING MINUTES

BioMarin Pharmaceuticals Inc.
Attention: Manisha Deshmukh
Senior Manager, Regulatory Affairs
105 Digital Drive
Novato, CA 94949

Dear Ms. Deshmukh:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Kuvan® (sapropterin dihydrochloride) Tablets.

We also refer to the telecon between representatives of your firm and the FDA on June 21, 2012. The purpose of the meeting was to discuss:

- BioMarin's plan to submit a prior approval supplement (PAS) to the Kuvan NDA to introduce an (b)(4) drug product formulation (powder for administration as an oral solution).
- Determine if the new Kuvan powder formulation qualifies for a Biowaiver.
- Obtain Agency agreement that the proposed manufacturing and stability plan for the new Kuvan powder formulation is acceptable.
- Obtain Agency agreement with the proposed final product label for the new Kuvan (b)(4) (primary packaging) and carton (secondary packaging) and whether the current physician package insert for Kuvan tablets can be updated with the powder formulation.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3877.

Sincerely,

{See attached electronic signature page}

Cathy Tran-Zwanetz
Regulatory Project Manager
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Chemistry

Meeting Date and Time: June 21, 2012 at 11:00 AM

Application Number: NDA 22181
Product Name: Kuvan® (sapropterin dihydrochloride) Tablets
Indication: reduce blood phenylalanine levels in patients with hyperphenylalaninemia due to tetrahydrobiopterin responsive phenylketonuria

Sponsor/Applicant Name: BioMarin

Meeting Chair: David Lewis, Ph.D.
Meeting Recorder: Cathy Tran-Zwanetz

FDA ATTENDEES

David Lewis, Ph.D., CMC Lead
Karen Riviere, Ph.D., Biopharmaceutical Reviewer
Cathy Tran-Zwanetz, Regulatory Health Project Manager

SPONSOR ATTENDEES

Arthur Blum, Vice President, Regulatory Affairs
Terry Milby, Director, Regulatory Affairs
Victoria Sluzky, Ph.D., Group Vice President, Quality and Process Development
Robert Baffi, Executive Vice President, Technical Operations
Doug Tingley, Director, Quality Control
Joyce Chou, Principal Scientist, Formulation Development

(b) (4)
Elizabeth Moyle, Director, Labeling
Manisha Deshmukh, Associate Director, Regulatory Affairs

NDA 22181
Meeting Minutes
Type C Meeting

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II

1.0 BACKGROUND

BioMarin has developed a new Kuvan powder formulation for administration as an oral solution to be packaged in a (b)(4) container closure system. (b)(4) will contain 100 mg active (sapropterin dihydrochloride) with a target fill weight of (b)(4). The contents (b)(4) (b)(4) can be dissolved in water or apple juice prior to administration. Thirty individual (b)(4) will be contained in a secondary carton.

The proposed powder formulation and the currently marketed Kuvan Tablet both contain identical levels of the active pharmaceutical ingredient, sapropterin dihydrochloride. Kuvan powder formulation is designed to improve the taste, flavor and appearance of sapropterin dihydrochloride in solution. The formulation contains (b)(4) (potassium citrate) and a sweetener (sucralose) which pleasantly masks the acidity and improves the palatability of sapropterin dihydrochloride in solution. The powder formulation comprises of ingredients that completely dissolve in water and offers the benefit of solution clarity upon powder dissolution.

The following topics will be discussed:

- BioMarin's plan to submit a prior approval supplement (PAS) to the Kuvan NDA to introduce (b)(4) drug product formulation (powder for administration as an oral solution).
- Determine if the new Kuvan powder formulation qualifies for a Biowaiver.
- Obtain Agency agreement that the proposed manufacturing and stability plan for the new Kuvan powder formulation is acceptable.
- Obtain Agency agreement with the proposed final product label for the new Kuvan (b)(4) (primary packaging) and carton (secondary packaging) and whether the current physician package insert for Kuvan tablets can be updated with the powder formulation.

Preliminary meeting responses were sent to the applicant on June 19, 2012. The applicant sent comments to the FDA's preliminary responses the evening of June 20, 2012. The FDA reviewed those documents.

2. DISCUSSION

Question 1: BioMarin has developed a new Kuvan powder formulation for administration as an oral solution which will be packaged (b)(4) container closure system. BioMarin believes that it qualifies for a Biowaiver as described in the briefing package.

Does the Agency agree that the Kuvan powder formulation for oral solution meets the Biowaiver requirements?

FDA RESPONSE:

There is insufficient information at this time to determine whether your proposed product is eligible for a waiver of the BA/BE CFR requirements. Please submit information/justification to address the following concerns:

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1. There is evidence in the scientific literature, although not totally conclusive, that sucralose may potentially affect the absorption and bioavailability of drugs (Abou-Donia et al. 2008, Brusica et al. 2009). This may apply to your product depending on the elimination pathway of sapropterin dihydrochloride.
2. Your proposed product (after it is dissolved in water or apple juice) may have a markedly different osmolarity compared to the reference product, potentially impacting the bioavailability of sapropterin dihydrochloride.

DISCUSSION:

Based on new data/information provided in the sponsor's response, FDA believes a biowaiver may be granted. However, final determination of the acceptance of the biowaiver will be made during the review of the NDA. FDA stated that the sponsor should include these data/information (response to bullet point numbers 1 and 2 above) as well as solubility data for the API and dissolution profile data for the proposed product in their NDA submission.

Question 2

BioMarin plans to submit a PAS to the Kuvan NDA for the Kuvan powder formulation. The following data will be provided in the supplement:

- Manufacturing data from two small scale registration/validation batches.
- One month of stability data for the two registration/validation batches and 3- months of supportive stability data (long term and accelerated) from an engineering batch.
- A commitment that a commercial/validation lot manufactured at the full scale will be placed on stability.

BioMarin believes that the above data supports approval of the (b)(4) presentation and an initial 18-month expiry date. Does the Agency agree?

FDA RESPONSE:

No, the standard stability unit to support post-approval changes is 3 months accelerated stability plus available long-term stability data. The registration/validation batches should be supported by three months accelerated and available long-term stability data from 3 batches, which are representative of your proposed commercial formulation/manufacturing process. The assignment of expiry for the new formulation will be a review issue.

DISCUSSION:

The applicant agreed to submit a stability dataset consisting of 3 months of accelerated and long-term stability data for three batches of drug product which are representative of the proposed commercial formulation and manufacturing process. The applicant agreed that the assignment of expiry was a review issue, not to be determined prior to receipt and review of the upcoming NDA.

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Question 3

Does the Agency agree with the proposed specifications?

FDA RESPONSE:

The proposed specifications appear to be reasonable. The acceptability of the specifications would be a review issue.

DISCUSSION:

Applicant agrees with the FDA response.

Question 4

BioMarin proposes to update the current physician package insert for Kuvan tablets (b)(4). Also BioMarin believes that the proposed final label for the Kuvan powder formulation (b)(4) (primary packaging – Attachment 1) and carton (secondary packaging – Attachment 2) are acceptable for commercial launch.

Does the Agency agree?

FDA RESPONSE:

This is to be reviewed jointly by ONDQA and OND with possible input from DMEPA. The acceptability of the proposed labels is a review issue.

DISCUSSION:

The FDA agreed to review the (b)(4) label prior to submission of the upcoming supplement. The FDA recognized the applicant's desire to commercialize the validation/exhibit batches along with the justification that the (b)(4) need to be printed prior to filling. The applicant was reminded that there is still a risk that the labels on the (b)(4) might be evaluated as inadequate.

3.0 ACTION ITEMS:

- FDA will follow up with User Fee Working group to verify that this can be submitted as a Prior Approval supplement.
- FDA will circulate the proposed label internally.

4.0 ATTACHMENTS AND HANDOUTS

Responses from applicant to the FDA's preliminary meeting response attached.

Kuvan (b)(4): BMRN responses to FDA Type C meeting Preliminary comments received on June 19, 2012

Question 1: BioMarin has developed a new Kuvan powder formulation for administration as an oral solution which will be packaged in (b)(4) primary container closure system. BioMarin believes that it qualifies for a Biowaiver as described in the briefing package.

Does the Agency agree that the Kuvan powder formulation for oral solution meets the Biowaiver requirements?

FDA RESPONSE:

There is insufficient information at this time to determine whether your proposed product is eligible for a waiver of the BA/BE CFR requirements. Please submit information/justification to address the following concerns:

1. There is evidence in the scientific literature, although not totally conclusive, that sucralose may potentially affect the absorption and bioavailability of drugs (Abou-Donia et al. 2008, Brusic et al. 2009). This may apply to your product depending on the elimination pathway of sapropterin dihydrochloride.

BIOMARIN RESPONSE dated June 20, 2012:

The composition of the Kuvan powder for oral solution is provided in the table below.

Composition of Kuvan powder for oral solution formulation

Ingredient	(b)(4)	
	mg/ (b)(4)	%, w/w
Sapropterin dihydrochloride	100.0	(b)(4)
Mannitol	(b)(4)	(b)(4)
Sucralose		
Potassium citrate		
Ascorbic acid		
Total		100.0

Based on a maximum Kuvan dose of 20 mg/kg, the amount of sucralose being administered with the (b)(4) formulation corresponds to (b)(4). This quantity is comparable to the dose (b)(4) reported to have no impact on the expression of P-gp, CYP3A and CYP2D1 by Abou-Donia et al., 2008. As the reviewers have pointed out, there is no consensus in the scientific literature about the potential influence of sucralose on the absorption and bioavailability of drugs, (for example Brusic et al., 2009, disagrees with the conclusions reached by Abou-Donia et al.). In any case, the amount of sucralose being co-administered with Kuvan is at a level which has been reported to have no adverse impact on absorption and bioavailability.

Sapropterin dihydrochloride is prone to rapid auto-oxidation in-vitro (Davis et al., 1987) and is rapidly eliminated via an oxidative pathway to 7, 8 dihydrobiopterin (BH₂) and biopterin (B) in-vitro at buffer pH comparable to plasma pH. Owing to its rapid auto-oxidation, cytochrome isoenzymes are unlikely to be involved in its elimination pathway. Regardless of its elimination pathway, the lack of effect of sucralose at the level present in the powder formulation on the cytochrome isoenzymes (CYP3A4 and CYP2D1) and P-gp expression suggests that the proposed powder formulation is not expected to influence the absorption and the clearance of sapropterin dihydrochloride.

2. Your proposed product (after it is dissolved in water or apple juice) may have a markedly different osmolarity compared to the reference product, potentially impacting the bioavailability of sapropterin dihydrochloride.

BIOMARIN RESPONSE dated June 20, 2012:

Osmolarity data for the commercial Kuvan tablets and the new powder formulation are presented in the table below. These data indicate that there is no significant difference in osmolarity between the commercial Kuvan tablet and the new proposed powder formulation.

Osmolarity of Kuvan tablet and (b)(4) dissolved in apple juice and water

Test Run	2 Kuvan tablets or (b)(4) dissolved in 20 ml water		2 Kuvan tablets or (b)(4) dissolved in 20 ml Apple juice	
	Tablets (mOsm/kg)	(b)(4) (mOsm/kg)	Tablets (mOsm/kg)	(b)(4) (mOsm/kg)
1	207	229	941	970
2	208	224	949	978
3	206	226	948	980
Average	207	226	946	976

Note that sapropterin dihydrochloride is administered with food. Therefore the final osmolarity of the ingested sapropterin dihydrochloride solution will vary with food consumed. Given the similar osmolarity of the dissolved powder and tablet formulations and the significant impact of food on osmolarity, no adverse impact on the absorption or bioavailability of sapropterin dihydrochloride is expected with the introduction of the (b)(4) formulation.

Question 2

BioMarin plans to submit a PAS to the Kuvan NDA for the Kuvan powder formulation. The following data will be provided in the supplement:

- o Manufacturing data from two small scale registration/validation batches.
- o One month of stability data for the two registration/validation batches and 3- months of supportive stability data (long term and accelerated) from an engineering batch.
- o A commitment that a commercial/validation lot manufactured at the full scale will be placed on stability.

BioMarin believes that the above data supports approval of the (b)(4) presentation and an initial 18-month expiry date. Does the Agency agree?

FDA RESPONSE:

No, the standard stability unit to support post-approval changes is 3 months accelerated stability plus available long-term stability data. The registration/validation batches should be supported by three months accelerated and available long-term stability data from 3 batches, which are representative of your proposed commercial formulation/manufacturing process. The assignment of expiry for the new formulation will be a review issue.

BIOMARIN RESPONSE dated June 20, 2012:

Taking into consideration the Agency response, BioMarin plans to submit three representative batches of Kuvan (b)(4) with three months of accelerated and long-term stability data to support 18-months expiry. Additional pilot-scale stability data will be provided to support the proposed expiry date. Process qualification and stability data will be submitted as a PAS under the current Kuvan NDA.

Question 3

Does the Agency agree with the proposed specifications?

FDA RESPONSE:

The proposed specifications appear to be reasonable. The acceptability of the specifications would be a review issue.

BIOMARIN RESPONSE dated June 20, 2012:

BioMarin has no further comments.

Question 4

BioMarin proposes to update the current physician package insert for Kuvan tablets (b)(4). (b)(4) Also BioMarin believes that the proposed final label for the Kuvan powder formulation (b)(4) (primary packaging – Attachment 1) and carton (secondary packaging – Attachment 2) are acceptable for commercial launch.

Does the Agency agree?

FDA RESPONSE:

This is to be reviewed jointly by ONDQA and OND with possible input from DMEPA. The acceptability of the proposed labels is a review issue.

BIOMARIN RESPONSE dated June 20, 2012:

The proposed label for the primary package (b)(4) must be printed prior to filling. BioMarin would appreciate receiving Agency feed-back regarding the suitability of the proposed label for the primary package to allow BioMarin to commercialize the registration/validation batches.

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5.0 CONCURRENCE

{See appended electronic signature page}

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Regulatory Health Project Manager for Quality
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

{See appended electronic signature page}

David Lewis, Ph.D.
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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.

/s/

CATHERINE A TRAN-ZWANETZ
07/20/2012

DAVID B LEWIS
07/20/2012
Minutes recorded and signed.