

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205065Orig1s000

OTHER REVIEW(S)

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title¹	KUVAN (sapropterin dihydrochloride) tablets, for oral use KUVAN (sapropterin dihydrochloride) powder, for oral solution
Applicant	Biomarin Pharmaceutical, Inc.
Application/Supplement Number	NDA 205065 NDA 22181, supplements 009, 010, (b) (4)
Type of Application	Original Submission Clinical Efficacy
Indication(s)	To reduce 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.
Office/Division	ODE III/DGIEP
Division Project Manager	Jessica Benjamin
Date FDA Received Application	NDA 205065 (February 8, 2013) NDA 22181, supplement 009 (February 25, 2013) NDA 22181, supplement 010 (February 26, 2013) (b) (4)
Goal Date	NDA 205065 (December 8, 2013) NDA 22181, supplement 009 (December 25, 2013) NDA 22181, supplement 010 (December 26, 2013) (b) (4)
Date PI Received by SEALD	December 17, 2013
SEALD Review Date	December 17, 2013
SEALD Labeling Reviewer	Jeanne M. Delasko
Acting SEALD Division Director	Sandra Kweder

¹ Product Title that appears in draft agreed-upon prescribing information (PI)

This Study Endpoints and Labeling Development (SEALD) Director sign-off review of the end-of-cycle, prescribing information (PI) for important format items reveals **outstanding format deficiencies** that should be corrected before taking an approval action. After these outstanding format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The Selected Requirements of Prescribing Information (SRPI) is a checklist of 42 important format PI items based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. The word “must” denotes that the item is a regulatory requirement, while the word “should” denotes that the item is based on guidance. Each SRPI item is assigned with one of the following three responses:

- **NO:** The PI does not meet the requirement for this item (**deficiency**).
- **YES:** The PI meets the requirement for this item (**not a deficiency**).
- **N/A:** This item does not apply to the specific PI under review (**not applicable**).

Selected Requirements of Prescribing Information

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- NO** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment: *Left margin is not 1/2 inch because "line listing numbers" are in the left margin. The same applies to the margin between the two columns with "line listing numbers." Remove all "line listing numbers" from HL, TOC and FPI.*

- YES** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- NO** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment: *Dosage Forms and Strengths heading is not in the center of the horizontal line, and the line does not extend over the entire width of the column.*

- NO** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *There is white space between each major heading; however, there should be NO white space between the HL heading and HL limitation statement. There must be NO white*

Selected Requirements of Prescribing Information

space between the product title and initial U.S. approval (i.e., the initial U.S. approval must be placed immediately beneath the product title.)

- NO** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment: *The reference "(2.1)" is missing for first bulleted item HL Dosage and Administration; also, the reference "(3)" is missing for the first and second bulleted items HL Dosage Forms and Strengths. Insert the missing references.*

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- NO** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment: *The heading is not bolded and must be bolded.*

Highlights Limitation Statement

- NO** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment: *For this statement, the name of the drug product should appear in upper case letters in both places as "KUVAN," not "Kuvan."*

Product Title in Highlights

Selected Requirements of Prescribing Information

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- YES** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- YES** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES

Selected Requirements of Prescribing Information

19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

- YES** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- "**See 17 for PATIENT COUNSELING INFORMATION**"

If a product **has** FDA-approved patient labeling:

- "**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**"
- "**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**"

Comment:

Revision Date in Highlights

- NO** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment: *Must state "Revised:12/2013," not "Revision Date: 12/2013."*

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
***Comment:** Delete the "line listing numbers" on the left edge and between the 2 columns. Also, there should be no periods after the section numbers in the TOC.*
- YES** 26. The following heading must appear at the beginning of the TOC: **“FULL PRESCRIBING INFORMATION: CONTENTS”**. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- NO** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
***Comment:** For subsection headings "5.6" and "8.6," the word "With" should be "with," (use lower case "w"). The same applies to FPI subsection headings 5.6 and 8.6. Also, subsection heading "6.2," in TOC and FPI, the word "From" should be "from" (i.e., lower case "f").*
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading **“FULL PRESCRIBING INFORMATION: CONTENTS”** must be followed by an asterisk and the following statement must appear at the end of TOC: **“*Sections or subsections omitted from the full prescribing information are not listed.”**
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- NO** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

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Comment: Cross reference, last paragraph, subsection 6.1 should read "[see Clinical Studies (14.1)], not "[see Study 5 in Clinical Studies (14.1)]." Also, subsection 6.3, second paragraph cross references subsection 5.5 regarding Phe-restricted diet, but the information is about hypersensitivity reactions (subsection 5.1) and hyperactivity (subsection 5.3). Ensure that the correct cross reference is used for this paragraph.

- NO** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment: Subsections 2.2 and 2.3 are listed in HL RMC; however, there is no vertical line on the left edge in the FPI to denote these changes. Insert the missing vertical lines. Also, subsection 5 is listed in HL RMC; however, in the FPI, there is only a vertical line for 3 sentences in subsection 5.3, one line in subsection 5.9, and two sentences in subsection 5.10. If these are the only RMC for subsection 5, you should reference (5.3, 5.9, 5.10) in HL RMC, not the entire W&P subsection [i.e., (5)].

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION**". This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), 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 practice."

Comment:

- YES** 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

Selected Requirements of Prescribing Information

“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.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

- [text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

JEANNE M DELASKO
12/17/2013

ERIC R BRODSKY
12/17/2013

I agree. Eric Brodsky, SEALD labeling team leader, signing for Sandra Kweder, acting SEALD Division Director.

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: December 10, 2013

To: Jessican Benjamin, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products (DGIEP)

From: Matthew Falter, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Pharm.D.
Group Leader, OPDP

Adewale Adeleye, Pharm.D., MBA
Regulatory Review Officer, OPDP

Subject: OPDP Labeling Consult Review

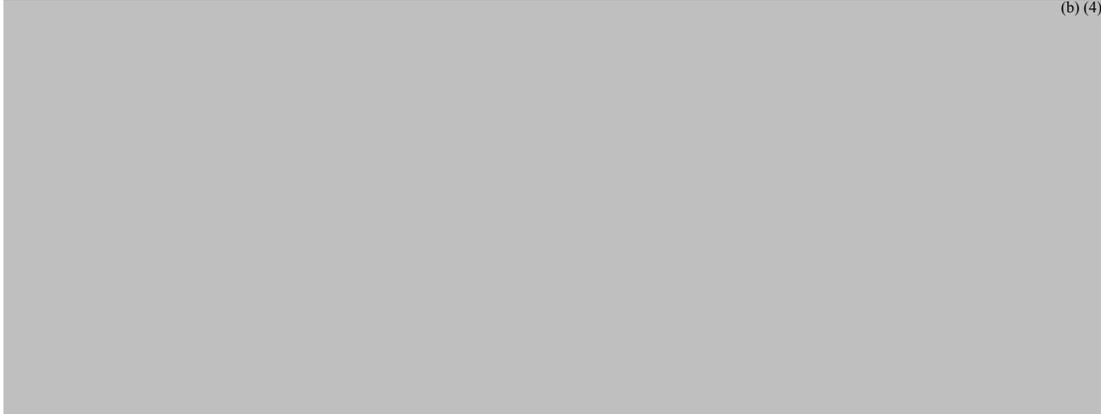
NDA 205065 – Kuvan (sapropterin dihydrochloride)
Powder for Oral Solution

NDA 22181/S-^{(b) (4)}, 009, 010 – Kuvan (sapropterin
dihydrochloride) Tablets

Reference is made to your April 17, 2013, and May 28, 2013, consult requests to OPDP requesting review of the Package Insert (PI), Patient Package Insert (PPI), and Carton and Container Labeling of the combined labeling for NDA 205065 – Kuvan (sapropterin dihydrochloride) Powder for Oral Solution and NDA 22181/S-^{(b) (4)} 009, 010 – Kuvan (sapropterin dihydrochloride) Tablets (Kuvan).

OPDP has reviewed the proposed PI. Our comments on the proposed PI are based on the proposed draft labeling titled “combined Kuvan label_clean.docx” available in the DGIEP eRoom on December 5, 2013 at 12:36pm (Version 29). Due to formatting issues, our comments on the proposed PI are provided both in the marked-up document attached and as follows:

Highlights:



Full Prescribing Information:

- 2.3 Instructions for Use (Line 245) – “The powder should dissolve rapidly and completely.”
 - **OPDP Comment:** We are concerned that the term 'rapidly' is vague and promotional in tone. We recommend including additional context [i.e. some measurement of time (average time or the longest time) it takes for the powder to dissolve] to better define the term 'rapidly'. Please see our comment in the PPI for similar concerns.



-  (b) (4) – “During clinical studies, gastritis was reported as a serious adverse reaction.”
 - **OPDP Comment:** We acknowledge that this language is in the previously approved label; however, we are concerned that the placement of this statement here may minimize the risk of gastritis. Specifically, if this is a serious adverse reaction, would it be better communicated to prescribers and patients as a Warning and Precaution?

Per 21 CFR 201.57(c)(6) – Warning and Precautions are by definition, serious (emphasis added), “This section must describe clinically significant adverse reactions (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug...”

- ^{(b) (4)} Post-Marketing Experience (Line 407-408) – “Most hypersensitivity reactions ^{(b) (4)}

- **OPDP Comment:** We are concerned that the phras ^{(b) (4)}

We recommend deleting this phrase.

- 17 Patient Counseling Information

- **OPDP Comment:** We are concerned that the language in this section in general is highly promotional in tone. According to the Labeling Review Tool, the section should focus on major risks of the drug and how the patient may mitigate or manage them and critical administration instructions or unique storage and handling instructions. OPDP recommends revising this section.



- 17.3 What Are the Benefits of Taking Kuvan? (Lines 742-746) – “Prolonged high blood Phe levels are neurotoxic and lead to impairment of intelligence and other brain functions (such as attentiveness). Reduction of blood Phe levels through dietary control is an important determinant of long-term neurologic outcome in PKU patients, and reduction of blood Phe levels in patients with PKU has been shown to decrease the long-term risk of neurologic injury”
 - **OPDP Comment:** While we acknowledge that this language is in previously approved labeling, we are concerned that this language can be used in promotional materials to overstate the efficacy of Kuvan. Specifically, this language in the context of a

promotional piece misleadingly implies that Kuvan has demonstrated efficacy on these endpoints. And while we acknowledge the statement in line 668, " ... long-term neurologic function in patients with PKU receiving Kuvan for the treatment of elevated blood Phe has not be assessed ... ," this would not mitigate any misleading impression within a promotional piece. OPDP recommends revising statements within the PI that imply efficacy in regards to neurological outcomes.

- 17.4 What Are the Risks of Taking Kuvan? (Lines 756-775) –
 - **OPDP Comment:** We are concerned that this presentation of risk information could be used in promotional materials in a manner that minimizes these risks. Specifically, we recommend revising this section to present risks in the same hierarchy as they are presented within the PI (i.e. Warnings and Precautions in the order listed in the PI followed by Adverse Reactions).



OPDP has reviewed the proposed Carton and Container Labeling for NDA 205065 submitted by the applicant on October 21, 2013 and available in the EDR at:

- <\\cdsesub1\evsprod\nda205065\0009\m1\us\114-labeling\1141-draft-labeling\11411-draft-carton-container-labels\kuvan-draft-carton-labels.pdf>
- <\\cdsesub1\evsprod\nda205065\0009\m1\us\114-labeling\1141-draft-labeling\11411-draft-carton-container-labels\kuvan-draft-packet-labels.pdf>

OPDP has also reviewed the proposed Carton Labeling for NDA 022181/S-009 submitted by the applicant on February 25, 2013 and available in the EDR at:

- <\\cdsesub1\evsprod\nda022181\0068\m1\us\spl\excellalabel.jpg>

OPDP has no comments on the proposed Carton and Container labeling in these applications at this time.

OPDP's review and comments on the proposed patient labeling (PPI and added IFU) was conducted jointly with the Division of Medical Policy Programs (DMPP). This review was submitted under separate cover and checked into DARRTS on December 10, 2013.

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions regarding this review, please contact Matthew Falter at (301) 796-2287 or matthew.falter@fda.hhs.gov.

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

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

/s/

MATTHEW J FALTER
12/10/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: December 10, 2013

To: Donna Griebel, MD
Director
Division of Gastroenterology and Inborn Error Products (DGIEP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Matthew Falter, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name), Dosage Form and Route, Application Type/Number, Supplement Number Kuvan (sapropterin dihydrochloride) Tablets, NDA 22-181/S-009, S-010, (b) (4)
Kuvan (sapropterin dihydrochloride) Powder for Oral Solution, NDA 205-065

Applicant: BioMarin Pharmaceuticals, Inc.

1 INTRODUCTION

On February 8, 2013 BioMarin Pharmaceuticals, Inc. submitted for the Agency's review a New Drug Application (NDA) 205-065 for Kuvan (sapropterin dihydrochloride) Powder for Oral Solution. The Applicant currently markets Kuvan (sapropterin dihydrochloride) Tablets under NDA 22-181. Kuvan (sapropterin dihydrochloride) Tablets were granted Orphan Product status on January 29, 2004 and were approved on December 13, 2007. The Applicant proposes the same indication for Kuvan (sapropterin dihydrochloride) Powder for Oral Solution that is approved for Kuvan (sapropterin dihydrochloride) Tablets: to reduce blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin- (BH4-) responsive Phenylketonuria (PKU). Kuvan (sapropterin dihydrochloride) Powder for Oral Solution and Kuvan (sapropterin dihydrochloride) Tablets will share common labeling.

The Applicant also submitted three Prior Approval Supplements (PAS) –Efficacy, to NDA 22-181/S-009, S-010, (b)(4), on February 25, February 26, and February 27, 2013, respectively. The purpose of these supplements is to revise the approved product labeling to allow tablet administration by intact swallowing in addition to the already approved method of dissolving the tablets in water or apple juice. The Applicant submitted results of several studies in support of their proposed labeling revisions.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Gastroenterology and Inborn Error Products (DGIEP) on April 17, 2013 and May 28, 2013 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for Kuvan (sapropterin dihydrochloride) Powder for Oral Solution and Kuvan (sapropterin dihydrochloride) Tablets respectively.

2 MATERIAL REVIEWED

- Draft Kuvan (sapropterin dihydrochloride) PPI received on April 17, 2013 and May 28, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 27, 2013 and December 2, 2013.
- Draft Kuvan (sapropterin dihydrochloride) Prescribing Information (PI) received on April 17, 2013 and May 28, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 27, 2013 and December 2, 2013.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- The "How should I take Kuvan" and "Instructions for Use" sections of the PPI incorporate DMPP and DMEPA comments

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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

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/s/

SHARON R MILLS
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Pediatric and Maternal Health Staff Review

Date: November 21, 2013

From: Carrie Ceresa, Pharm D, MPH
Regulatory Reviewer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Jeanine Best, MSN, RN, PNP
Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff

Lynne P. Yao, M.D., OND Associate Director,
Pediatric and Maternal Health Staff

To: The Division of Gastroenterology and Inborn Errors Products (DGIEP)

Drug: Kuvan (sapropterin dihydrochloride) tablets and powder for oral solution

NDA: 22-181/S-009, 010, (b)(4) & 205-065 (combined label)

Subject: Labeling revisions with regard to pregnancy and nursing mothers sections

Applicant: BioMarin Pharmaceuticals Inc.

Materials Reviewed: August 30, 2013, combined labeling submitted by the sponsor

Consult Question: “DGIEP is conducting a combined labeling review for two NDAs. DGIEP requests that PMHS provides input on updating the labeling for Kuvan to meet the latest requirements for pregnancy and reproductive information in product labeling.”

INTRODUCTION

Kuvan (sapropterin dihydrochloride) tablets were initially approved on December 13, 2007, for the reduction of blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin- (BH4-) responsive Phenylketonuria (PKU). Kuvan is also to be used in conjunction with a Phe-restricted diet.

BioMarin Pharmaceuticals, Inc., submitted NDA 22-181 efficacy supplements 009, 010 (b) (4) for Kuvan for the tablet dosage form on February 21, 26 and 27 of 2013, and original New Drug Application NDA 205-065 for the powder for oral solution dosage form on February 8, 2013. The Division of Gastroenterology and Inborn Error Products (DGIEP) requested that BioMarin combine the draft prescribing information for both dosage forms from each of the submissions referenced above into one single draft.

NDA 22-181 efficacy supplement 009 was submitted to include new administration directions. Specifically, labeling will be revised to allow for tablets to be swallowed intact, in addition to the already approved administration method of dissolving the tablets in water or apple juice. NDA 22-181 efficacy supplement 010 was submitted to add information on the effects of Kuvan to the cardiac QT Interval and to update the post marketing safety information in the Kuvan labeling. (b) (4)

The Division of Gastroenterology and Inborn Error Products (DGIEP) consulted the Pediatric and Maternal Health Staff – Maternal Health Team (PMHS-MHT) to review and update the Pregnancy and Nursing Mothers information in the Kuvan labeling.

This review provides recommended revisions and structuring of existing information related to the Pregnancy and Nursing Mothers labeling in order to provide clinically relevant information for prescribing decisions and to comply with current regulatory requirements.

BACKGROUND

Kuvan (sapropterin dihydrochloride)

Kuvan is a synthetic form of the dihydrochloride salt of naturally occurring tetrahydrobiopterin (BH4), the cofactor for the enzyme phenylalanine hydroxylase (PAH).¹ PAH hydroxylates Phe through an oxidative reaction to form tyrosine. PAH activity is absent or deficient in patients with phenylketonuria (PKU). Treatment with Kuvan appears to activate residual PAH enzyme, improve the normal oxidative metabolism of Phe and decrease Phe levels in some patients.

Phenylketonuria (PKU)

Phenylketonuria (PKU) has an incidence in the United States of about 1 in 10,000 to 15,000.² PKU is a recessive disorder that is caused by absence or decreased activity of the phenylalanine hydroxylase enzyme.² Elevated blood levels of phenylalanine lead to the signs and symptoms of PKU and include delayed development, seizures, behavioral problems, psychiatric disorder and intellectual disabilities. Error! Bookmark not defined.

¹ Approved Kuvan (sapropterin dihydrochloride) package insert.

² Marcason, W. (2013). Is There a Standard Meal Plan for Phenylketonuria (PKU)? *Journal of the Academy of Nutrition and Dietetics*, 118 (8), 1124.

Phenylketonuria (PKU) and pregnancy

Maternal PKU, if untreated, can lead to congenital heart disease, dysmorphic features, intrauterine growth retardation or microcephaly in the child.^{3,4} The Maternal Phenylketonuria Collaborative Study (MPKUCS; Rouse, 1997) was conducted to evaluate the effects of PKU and dietary control during pregnancy.⁴ There were 468 pregnancies followed in the study, and of those, 331 resulted in live births.⁴ Pregnancy terminations occurred in 28% of pregnancies; 13% were documented as spontaneous abortions and 15% were elective terminations.⁴ The authors concluded that uncontrolled levels of phenylalanine above 600 umol/L were associated with fetal abnormalities such as facial defects, growth and neurological abnormalities and congenital defects of the heart.⁴ The authors also concluded that strict dietary control of phenylalanine levels during pregnancy is essential in reducing possible teratogenic effects.⁴

DISCUSSION

Pregnancy and Nursing Mothers Labeling

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in milk is noted and presented in nursing mothers labeling, not the amount. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a subsection, Females and Males of Reproductive Potential.

The Drugs and Lactation Database (LactMed)⁵ was searched for available lactation data on with the use of Kuvan and sapropterin dihydrochloride, and no information was located. The LactMed database is a National Library of Medicine (NLM) searchable database with information on drugs and lactation. The LactMed database provides information when available on maternal levels in breastmilk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered, and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

³ Koch, R. (2008). Maternal Phenylketonuria and Tetrahydrobiopterin. *Pediatrics*, 122, 1369.

⁴ Rouse, B., Azen, C., Koch, R., Matalon, R., Hanley, W., de la Cruz, F., et al. (1997). Maternal Phenylketonuria Collaborative Study (MPKUCS) Offspring: Facial Anomalies, Malformations, and Early Neurological Sequelae. *American Journal of Medical Genetics* 69, 89-95.

⁵ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>

The December 13, 2007, approval letter for NDA 22-181 includes Post Marketing Commitment number 4 which commits Biomarin Pharmaceuticals to designing and implementing a registry of patients with PKU being treated with Kuvan (sapropterin dihydrochloride) that will obtain long term clinical status information, such as patient demographics, clinical status, specifics of treatment, neurocognitive, assessments, growth and development and adverse events. In addition, the sponsor committed to conduct a sub-study within the registry that will evaluate the effects of Kuvan on pregnancy and lactation. In response to this commitment the sponsor is conducting the Phenylketonuria (PKU) Demographic, Outcomes and Safety Registry (PKUDOS) which is a registry for patients with a confirmed diagnosis of PKU with hyperphenylalaninemia who have either received Kuvan therapy or currently receiving Kuvan therapy, or intend to begin receiving Kuvan therapy within 90 days of entering the registry. The PKUDOS program is a voluntary, multicenter, observational program. In addition, the sponsor is also conducting the PKU MOMS subregistry which collects data on patients with PKU who are pregnant at enrollment in the registry or who become pregnant while participating in the PKUDOS registry. The sponsor has committed to submitting interim registry data annually and the final study report for submission is due May 25, 2025. (b) (4)



CONCLUSION

The pregnancy subsection of the Kuvan labeling was structured in the spirit of the proposed PLLR, while complying with current labeling regulations. The nursing mothers subsection of labeling was revised to comply with current labeling recommendations.

The PMHS-MHT discussed labeling recommendations with the review team during a labeling meeting on November 7, 2013. The following PMHS- MHT recommendations reflect the discussions with the Division at that meeting.

PMHS LABELING RECOMMENDATIONS

PMHS-MHT labeling excerpts are below with deleted text shown with a strikethrough and new text as underlined.

HIGHLIGHTS OF PRESCRIBING INFORMATION

 (b) (4)

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

A patient registry has been established that also collects data on women who are treated with Kuvan during pregnancy. For more information regarding the registry program call 1-866-906-6100.

Risk Summary

There are no adequate and well-controlled studies with Kuvan in pregnant women. An embryo-fetal development study with sapropterin dihydrochloride in rats using oral doses up to 3 times the maximum recommended human dose (MRHD) given during the period of organogenesis showed no effects. In a rabbit study using oral administration of sapropterin dihydrochloride during the period of organogenesis, a rare defect, holoprosencephaly, was noted at 10 times the MRHD. Kuvan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Disease-associated maternal and/or embryofetal risk

Available data from the Maternal Phenylketonuria Collaborative Study on 468 pregnancies and 331 live births in PKU-affected women demonstrated that uncontrolled Phe levels above 600 $\mu\text{mol/L}$ are associated with a very high incidence of neurological, cardiac, facial dysmorphism, and growth anomalies. Good dietary control of Phe levels during pregnancy is essential to reduce the incidence of Phe-induced teratogenic effects.

Animal Data

No effects on embryo-fetal development were observed in a reproduction study in rats using oral doses of up to 400 mg/kg/day sapropterin dihydrochloride (about 3 times the MRHD of 20 mg/kg/day, based on body surface area), administered during the period of organogenesis. However, in a rabbit reproduction study, oral administration of a maximum dose of 600 mg/kg/day (about 10 times the MRHD, based on body surface area) during the period of organogenesis was associated with (b) (4) statistically significant (b) (4) in the incidence of holoprosencephaly, (b) (4).

(b) (4)

(b) (4)

(b) (4)

8.3 Nursing Mothers

It is not known whether Kuvan is present in human milk. Sapropterin is present in the milk of intravenously-, but not orally-treated lactating rats. The developmental and health benefits of human milk feeding should be considered along with the mother's clinical need for Kuvan and any potential adverse effects on the human milk-fed child from the drug or from the underlying maternal condition. Exercise caution when Kuvan is administered to a nursing woman.

(b) (4)

17.5 BioMarin PKU Disease Registry ^(b)₍₄₎

BioMarin established a product registry for PKU patients that also collects data on women who become pregnant while receiving Kuvan treatment.

(b) (4)

Reviewer comment: PMHS-MHT refers to the final NDA action for final labeling.

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/s/

CARRIE M CERESA
11/21/2013

JEANINE A BEST
11/21/2013

LYNNE P YAO
11/25/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: October 24, 2013

Reviewer: Lisa V. Khosla, PharmD, M.H.A
Division of Medication Error Prevention and Analysis

Team Leader: Lubna Merchant, M.S., PharmD
Division of Medication Error Prevention and Analysis

Drug Name(s) and Strength(s): Kuvan (Sapropterin Dihydrochloride) Tablets, 100 mg
Kuvan (Sapropterin Dihydrochloride)
Powder for Oral Solution, 100 mg

Application Type/Number/Submission: NDA #22181/ S-009, S-010, (b) (4)
NDA #205065

Applicant/Sponsor: BioMarin Pharmaceutical Inc.

OSE RCM #: 2013-769 and 2013-1231

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review responds to a request from the Division of Gastroenterology and Inborn Error Products (DGIEP) to evaluate the Applicant's proposed container label, carton labeling, and full prescribing information for Kuvan (Sapropterin dihydrochloride) NDA 205065 for areas of vulnerability that could lead to medication errors. DGIEP requested this review as part of their evaluation for the addition of a new dosage form; powder for oral solution, to the Kuvan product line. Additionally, the Applicant submitted labeling supplements which propose to add whole tablet administration to the labels and labeling for Kuvan NDA 22181/S-009, S-010, (b)(4) which is also evaluated in this review.

1.1 PRODUCT INFORMATION

Table 1 provides product information for Kuvan tablet and Kuvan powder for oral solution. The product information is obtained from the combined product labeling of Kuvan tablet (NDA 22181) and Kuvan powder for oral solution (NDA 205065) submitted on September 5, 2013:

Table 1. Product Information for Kuvan (Sapropterin Dihydrochloride)		
Application	Currently Marketed Approved December 13, 2007 NDA 022181	Proposed NDA 205065
Active Ingredient:	Sapropterin dihydrochloride	Sapropterin dihydrochloride
Indication of Use:	Reduce 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.	Reduce 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.
Route of Administration:	Oral	Oral
Dosage Form:	Tablet	Powder for oral solution
Strength:	100 mg	100 mg
Administration:	Tablets may be swallowed whole or dissolved in 4 to 8 oz. (120-240 mL) of water or apple juice and taken within 15 minutes.	Powder for oral solution should be dissolved in 4 to 8 oz. (120-240 mL) of liquid and consumed within 30 minutes of preparation.

Dose and Frequency:	5 mg/kg to 20 mg/kg once a day at the same time with food.	5 mg/kg to 20 mg/kg once a day at the same time with food.
How Supplied:	Bottles of 30 tablets and 120 tablets	Carton of 30 unit dose packets and single unit dose packets
Storage:	Room Temperature	Room Temperature

2 METHODS AND MATERIALS REVIEWED

We searched the FDA Adverse Event Reporting System (FAERS) database for Kuvan medication error reports using the strategy listed in Table 2. The description of the FAERS database is provided in Appendix A. We also reviewed the container label, carton labeling, and Full Prescribing Information submitted by the Applicant for Kuvan tablet and Kuvan powder for oral solution.

2.1 SELECTION OF MEDICATION ERROR CASES

DMEPA searched the FAERS database using the strategy listed in Table 2.

Table 2: FAERS Search Strategy	
Date	April 24, 2013
Drug Names	Active Ingredient: Sapropterin Dihydrochloride and Sapropterin Product Name: Kuvan
MedDRA Search Strategy	Medication Errors HLT Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT
Time Limitation	None

This search strategy yielded ten reports. Each report was reviewed for relevancy and duplication. The NCC MERP Taxonomy of Medication Errors was used to code the case outcome and error root causes when provided by the reporter¹. Appendix G provides listings of all case numbers for the cases summarized in this review.

After individual review, 6 reports were not included in the final analysis as they did not involve a medication error.

¹ The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>. Accessed June 1, 2011.

2.2 ISMP PUBLICATION SEARCH

We searched the ISMP publications on October 8, 2013 for additional cases and actions concerning Kuvan. No additional cases were found.

2.3 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,² along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Label for Kuvan tablet submitted April 3, 2013 (Appendix B)
- Carton Labeling for Kuvan tablet submitted April 3, 2013 (Appendix C)
- Container Label for Kuvan powder for oral solution submitted October 21, 2013 (Appendix D)
- Carton Labeling for Kuvan powder for oral solution submitted October 21, 2013 (Appendix E)
- Full Prescribing Information (combined Kuvan tablet and Kuvan powder for oral solution) submitted September 5, 2013 (Appendix H)
- Currently marketed carton labeling of Kuvan tablet from DailyMed website (Appendix F)

3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our FAERS search and the risk assessment of the Kuvan product design as well as the associated label and labeling.

3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, four Kuvan medication error cases remained for our detailed analysis.

Wrong Technique Errors (n=2): In both cases, Kuvan tablets were swallowed whole instead of dissolved prior to administration. One patient did not report any adverse events and the other patient reported stomach aches which resolved by morning. No contributing factors were reported. We note that the Applicant is now proposing to add the whole tablet administration to the prescribing information.

Wrong Dose Errors (n=2): The first case involved a patient who took the wrong number of tablets at breakfast, lunch, and dinner because she misunderstood the dosage instructions. She felt mild stomach discomfort which went away at the end of the day.

The second case involved a 5 year-old patient who received the wrong dose because the dose was calculated based on the patient's weight in pounds instead of kilograms. Patient

² Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

labs were normal and hyperactivity resolved once the dose was corrected. We note that the prescribing information clearly states the dose calculation based on kilograms.

4 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESMENT

The Applicant is proposing a new dosage formulation of Kuvan powder for oral solution to provide an alternative to tablets for patients. The powder for oral solution has the same indication, dosage, and strength as the tablet formulation. Additionally, the powder for oral solution should be dissolved in 4 to 8 ounces of liquid prior to administration similar to currently approved Kuvan tablets. Moreover, the Applicant is proposing to add the option of swallowing whole tablets of Kuvan to the administration instructions. The combined Full Prescribing Information of Kuvan tablets and Kuvan powder for oral solution provides the proposed revisions.

Although Kuvan powder for oral solution has the same active ingredient as Kuvan tablet, it is a new dosage form and we want to ensure that the labels and labeling properly mitigate any potential medication error risks associated with the addition of this new dosage form. Therefore, we performed a risk assessment of the proposed Full Prescribing Information to identify deficiencies that may lead to medication errors. We note that the “liquid” used for dissolution of Kuvan powder for oral solution needs to be specified.

We also reviewed the container label and carton labeling of Kuvan powder for oral solution and found them adequate.

5 CONCLUSIONS

DMEPA concludes that the proposed container label and carton labeling of Kuvan powder for oral solution are acceptable. However, the Full Prescribing Information can be improved to clarify important information regarding dissolution of the powder prior to administration. We made recommendations in section 6 that could help promote the safe use of the product and to mitigate any confusion.

If you have further questions or need clarifications, please contact Phong Do, OSE Regulatory Project Manager, at 301-796-4795.

6 RECOMMENDATIONS

Based on this review, we have made revisions to the Full Prescribing Information for review and consideration by DGEIP. See Appendix H for details.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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/s/

LISA V KHOSLA
10/24/2013

LUBNA A MERCHANT
10/24/2013

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Application: NDA 205065

Application Type: New NDA

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

Applicant: BioMarin

Submission Date: 2/7/2013

Receipt Date: 2/8/2013

1.0 Regulatory History and Applicant's Main Proposals

Kuvan is indicated for the reduction of blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin-(BH4) responsive phenylketonuria (PKU).

BioMarin currently markets an approved Kuvan Tablet under NDA 22181. This NDA provides for a new powder formulation for the same indication to be packaged in a unit dose packet for administration as an oral solution. It is designed to improve the taste, flavor, and appearance of Kuvan.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by June 24, 2013. The resubmitted PI will be used for further labeling review.

4.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- NO** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment: *margins greater than 1/2 inch*

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- NO** 4. White space must be present before each major heading in HL.

Comment: *No white space between RCM and Indications and Usage*

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

Selected Requirements of Prescribing Information (SRPI)

YES

6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

YES

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

Comment:

Product Title

YES

10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

YES

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

N/A

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

12. All text must be **bolded**.

Comment:

N/A 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

N/A 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

YES 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

YES 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

NO 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment: *only subheadings are marked*

YES 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

N/A 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment:

Dosage Forms and Strengths

Selected Requirements of Prescribing Information (SRPI)

- YES** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

YES

Selected Requirements of Prescribing Information (SRPI)

30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

- YES** 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

- YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment:

- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

- YES** 37. All section and subsection headings and numbers must be **bolded**.

Comment:

- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use

Selected Requirements of Prescribing Information (SRPI)

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- NO** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

- YES** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- YES** 45. If no Contraindications are known, this section must state “None”.

Selected Requirements of Prescribing Information (SRPI)

Comment:

Adverse Reactions

- NO** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), 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.”

Comment:

- NO** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), 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.”

Comment:

Patient Counseling Information

- NO** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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
06/03/2013

RICHARD W ISHIHARA
06/04/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 205065 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Kuvan Established/Proper Name: sapropterin dihydrochloride Dosage Form: powder for oral solution Strengths: 100 mg		
Applicant: BioMarin Agent for Applicant (if applicable):		
Date of Application: February 7, 2013 Date of Receipt: February 8, 2013 Date clock started after UN:		
PDUFA Goal Date: December 8, 2013		Action Goal Date (if different): December 6, 2013
Filing Date: April 9, 2013		Date of Filing Meeting: March 19, 2013
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 3		
Proposed indication(s)/Proposed change(s): reduction of Phe levels in patients with HPA due to BH4 responsive PKU		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): NDA 22181				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>																				
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1482 1349 1623"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>		<p>X</p>		<p>The sponsor has 7 years of marketing exclusivity ending in</p>																

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				12/2014 for the same product under NDA 22181.
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>		X		
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDA/NDA efficacy supplements only</i>) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>		X		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDA only</i>)?		X		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>		X		

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDA/NDA efficacy supplements</i>) or under 21 CFR 601.2	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

(BLAs/BLA efficacy supplements) including:				
<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?		X		No clinical or BE studies included with application
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?		X		No clinical trials
<i>If yes, ensure that the application is also coded with the</i>				

<i>supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>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..."</i>	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	X			
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>			X	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		X		Orphan designation
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>				
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>				
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?</p> <p><i>If no, request in 74-day letter</i></p>				
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i></p>		X		
<p><u>Proprietary Name</u></p> <p>Is a proposed proprietary name submitted?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i></p>	YES	NO	NA	Comment
		X		OSE contacted sponsor
<p><u>REMS</u></p> <p>Is a REMS submitted?</p> <p><i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i></p>	YES	NO	NA	Comment
		X		
<p><u>Prescription Labeling</u></p> <p>Check all types of labeling submitted.</p>	<input type="checkbox"/> Not applicable			
	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send <i>WORD</i> version if available)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)		X		
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):		X		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): Type C meeting – 6/21/2012	X			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		X		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 19, 2013

BLA/NDA/Supp #: NDA 205065

PROPRIETARY NAME: Kuvan

ESTABLISHED/PROPER NAME: sapropterin dihydrochloride

DOSAGE FORM/STRENGTH: powder for oral solution; 100mg

APPLICANT: BioMarin

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): reduction of Phe levels in patients with HPA due to BH4 responsive PKU

BACKGROUND: BioMarin currently markets an approved Kuvan Tablet under NDA 22181. They have developed a new powder formulation for the same indication to be packaged in a unit dose packet for administration as an oral solution. It is designed to improve the taste, flavor, and appearance of Kuvan.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jessica Benjamin	Y
	CPMS/TL:	Wes Ishihara	N
Cross-Discipline Team Leader (CDTL)	Marie Kowblansky		Y
Clinical	Reviewer:		
	TL:	Lara Dimick	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial</i>)	Reviewer:		

<i>products)</i>			
	TL:		
Clinical Pharmacology	Reviewer:	Insook Kim	Y
	TL:	Sue Chih Lee	N
Biostatistics	Reviewer:		
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Eddie Ng	Y
	TL:	David Joseph	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Caroline Strasinger	Y
	TL:	Marie Kowblansky	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Biopharmaceutics – Kelly Kitchens		Y
Other attendees	Andrew Mulberg, Deputy Director		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain: no clinical sites</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> 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? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input checked="" type="checkbox"/> Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input checked="" type="checkbox"/> N/A <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Andrew Mulberg</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V):</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter

<input type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]</p>
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
- (3) 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) 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, and.
- (3) 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) 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, or
- (3) 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 OND ADRA or OND IO.

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
04/17/2013