CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205065Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	December 18, 2013
From	Andrew E. Mulberg, MD, FAAP, CPI
Subject	Division Deputy Director Summary Review
NDA/BLA # Supplement #	22-181: S009/S010/ (b) (4) 205065
Applicant Name	BioMarin
Date of Submission	2/25, 26, 27/2013
PDUFA Goal Date	12/25/2013
Proprietary Name / Established (USAN) Name	Sapropterin (Kuvan®)
Dosage Forms / Strength	Powder – 100mg packets 5, 10, or 20 mg/kg/day
Proposed Indication(s)	Reduction of blood Phe levels in patients with hyperphenylalaninemia due to BH_4-responsive hyperphenylananemia
Action/Recommended Action for NME:	**Approval** of Efficacy Supplements S009 and S010 (b) (4)

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Carla Epps, MD
CDTL Reviews: Supplements 9 and 10: Supplement 11:	 Marie Kowblansky, PhD Lara Dimick, MD
Clinical Pharmacology Review	Insook Kim, Ph.D.
Nonclinical Reviewer	Yuk-Chow Ng, Ph.D.
Biopharmaceutics reviewer	Kelly M. Kitchens, Ph.D.
Clinical Pharmacology Team Leader	Insook Kim, Ph.D.
ONDQA	Caroline Strasinger, Ph.D.

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

BioMarin currently markets Kuvan® (sapropterin hydrochloride) for the following indication:

1) Kuvan® is indicated for reduction of blood Phe levels in patients with hyperphenylalaninemia due to BH_4-responsive phenylketonuria (PKU).

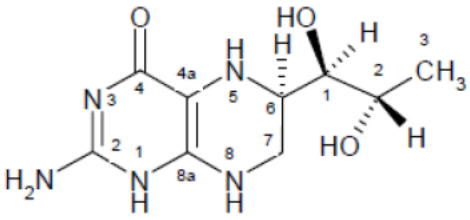
In these NDA supplements, the applicant proposes changes to the package insert utilizing data from several supplements to NDA 022-181. Efficacy Supplement 9 included the results of a relative bioavailability study (PKU-013) and a post-hoc pharmacodynamics analysis (b) (4) that evaluated the comparability of two methods of administration (dissolved vs. intact tablets) of Kuvan®. The applicant proposes to change labeling to allow administration of Kuvan® as intact tablets; the current labeling only allows administration of dissolved tablets. Supplement 10 included the results of a TQT study (QTC-001) that was conducted to fulfill Post-marketing Commitment (PMC) #5. The applicant proposes to update labeling to include information on the TQT study results. (b) (4)

Previous clinical studies involved with Kuvan® included efficacy and Kuvan® safety of Kuvan® was evaluated in 4 clinical studies in patients with PKU ages 4 to 48 years. Study 1 was an 8-day open-label uncontrolled enrichment study conducted in patients with PKU who were not on dietary restriction and was designed to identify patients for further study in a controlled efficacy trial. Of 489 patients (age range 8-48 years); 96 patients (20%) were determined to be responsive to treatment with Kuvan® (defined as $\geq$30% decrease in blood Phe). Study 2 was the pivotal study for Kuvan® and was a 6-week double-blind, placebo-controlled trial in 88 patients with PKU. The primary endpoint for the trial was mean change in blood Phe level. Study 3 was a 6-week open-label, extension trial in 80 patients who were identified as responders to Kuvan® in Study 1 and completed study 2. Patients were treated for 3 consecutive 2-week courses with 3 different doses of Kuvan® (5, 10, and 20 mg). Study 4 was an 8-day, open-label, uncontrolled diet study conducted in pediatric patients (age range 4-12 years) with PKU who were on a Phe-restricted diet. Of 89 patients, 50 patients (56%) were determined to be responders. Because these were short-term trials, the long-term efficacy of Kuvan® on blood Phe levels remains unknown. In addition, these clinical trials did not evaluate the efficacy of Kuvan® on neurocognitive, growth and development, or nutritional status.

2. Background

Kuvan® is a formulation of sapropterin dihydrochloride. The structural formula for Kuvan® is pictured below:

6R Form (Active) – 4(1H) conformation



• 2 HCl

Kuvan® Tablets was approved in 2007 under NDA 22-181, and is indicated for the treatment of hyperphenylalaninemia (HPA) due to tetrahydrobiopterin-(BH_4) responsive phenylketonuria (PKU). An Established Pharmacologic Class has not been assigned to this product. The Sponsor proposes "phenylalanine hydroxylase (b) (4) activator" as the Established Pharmacologic Class (EPC) text phrase for sapropterin dihydrochloride.

The active ingredient in Kuvan® is sapropterin dihydrochloride, which is a synthetic form of tetrahydrobiopterin (BH_4). It has been well established that BH_4 is an essential co-factor for PAH (phenylalanine hydroxylase), and is critical in the conversion of phenylalanine (Phe) to tyrosine[1] (). In patients with hyperphenylalaninemia due to BH_4-responsive phenylketonuria, treatment with Kuvan® activates residual PAH enzyme activity, improves the normal oxidative metabolism of Phe, and decreases blood Phe levels in these patients. Thus, Kuvan® is considered a cofactor and activator of the enzyme PAH. The proposed EPC text phrase is appropriate as it is based on the mechanism of action of sapropterin, and therefore is scientifically valid. In addition, the medical team concurs that the proposed classification is clinically meaningful.

The supplementary trial results submitted for this application were submitted to address additional labeling from the original NDA including addressing comparability of two methods of administration (dissolved vs. intact tablets) of Kuvan®, labeling to include information on the TQT study results to fulfill PMC #5 (b) (4)

(b) (4)

(b) (4)

[1] Heintz et. al., Human Mutation 2013, 34, 927.

(b) (4)

PKU-006 was a two-part trial to evaluate safety and efficacy of Kuvan® in PKU patient's ages 4 to 12 years old following increased dietary Phe intake. Part 1 was an 8-day, open-label treatment period designed to identify PKU patients who were BH_4-responsive. Part 2 was a 10-week, double-blind, randomized, placebo-controlled trial during which BH_4-responders received incremental increases in dietary Phe while being treated with a stable (20 mg/kg/day) dose of Kuvan®.

These data were proposed to update the following sections of the label according to PLR conversion including Section 2 Dosage and Administration, Section 6 Adverse Reactions (including sections 6.1 Clinical Trials Experience,, and 6.3 Postmarketing Experience), Section 10 Overdosage, Sections 12.2 and 12.3 pharmacokinetics, and Section 14 Clinical Studies of the current product labeling. Further discussion of regulatory history is provided in the CDTL summary.

3. CMC

The ONDQA reviewer clearly stated that "This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. An overall "Acceptable" recommendation has ***not*** been made by the Office of Compliance. All labels and labeling (Description and How Supplied sections) have not been finalized yet. Therefore, from the ONDQA perspective, this NDA is not ready for approval in its present form per 21 CFR 314.125(b) (6), (13) until the pending issues are resolved."

The analytical procedures are the same as those used for the approved KUVAN® tablets (NDA 22181). The adequacy of using the same dissolution method is being reviewed by the Biopharmaceutics reviewer Dr. K. Kitchens.

The Applicant's bases for a biowaiver request are summarized below:

1. The powder formulation delivers an identical quantity of active pharmaceutical ingredient (b) (4) the primary excipient, mannitol, as the tablet formulation-see Table 1 below.
2. Sapropterin dihydrochloride is very soluble in aqueous solutions (greater than 1 g/mL) and exhibits rapid dissolution.
3. The excipient sucralose, which is present in the powder formulation but not in the tablet formulation, does not affect drug absorption and bioavailability.
4. The osmolarity of Kuvan® Powder is similar to that of Kuvan® Tablets in water and in apple juice.

Table 1: Comparison of Formulation of Kuvan®

Ingredient	Kuvan Powder Formulation for Oral Solution		Kuvan Tablet	
	%	Amount per packet (mg)	%	Amount per tablet (mg)
Sapropterin dihydrochloride	(b) (4)	100.0	(b) (4)	100.00
Mannitol		(b) (4)		(b) (4)
Crospovidone				
Dibasic Calcium Phosphate	(b) (4)			
Riboflavin	(b) (4)			
Sodium Stearyl Fumarate				
Sucralose				
Potassium Citrate				
Ascorbic acid				
Total	100.0%		100.00%	

Solvent	Solvent required for 1 g of solute	Solubility
Water	Less than 1 mL	Very soluble
	(b) (4)	Very soluble
		Very soluble
		Sparingly soluble
		Very slightly soluble
		Practically insoluble

T.S. = test solution

Overall Conclusions:

- The Kuvan® powder formulation contains the same active ingredient in the same concentration as the Kuvan® tablet formulation.
- Kuvan® Powder is highly soluble in aqueous solution.
- Kuvan® Powder exhibits rapid dissolution (i.e. (b) (4)% dissolved in 5 minutes) using the dissolution method for Kuvan® Tablets.
- Kuvan® Powder has similar osmolarity as Kuvan® Tablets in water and apple juice.
- The inactive ingredients in the powder formulation are not expected to affect drug absorption and bioavailability.
- The amount of sucralose in the powder formulation is acceptable and is not expected to affect drug absorption and bioavailability.
- The waiver for in-vivo bioavailability/bioequivalence studies is granted.

Based on the information submitted for the composition, solubility, and osmolarity of Kuvan® (sapropterin dihydrochloride) Powder for Oral Solution, the waiver for in-vivo

bioavailability/bioequivalence studies is granted. From the Biopharmaceutics perspective, NDA 205065 for Kuvan® (sapropterin dihydrochloride) Powder for Oral Solution is recommended for approval.

In total the list of deficiencies from the CMC reviewer include the following to be communicated to the Sponsor:

A. Facility Inspections
   - The Office of Compliance has not issued "Acceptable" recommendation yet.

B. Labels/Labeling
   - In the Highlights Section:
     Present the Dosage Form and Strengths as Follows:
     Tablet, 100 mg
     Powder for Oral Solution, 100 mg
   - In the Description Section:
     Include the Pharmacological/therapeutic class in the description. Suggested text would be:

     KUVAN® (sapropterin dihydrochloride) is an orally administered Phenylalanine Hydroxylase (b) (4) *activator (or PAH* (b) (4) *activator)*

   - For the Immediate Container Closure and the Carton:
     Alter the equivalency statement to read:

**100 mg sapropterin dihydrochloride equivalent to 76.8 mg of sapropterin*

4. Nonclinical Pharmacology/Toxicology

There are no new nonclinical issues raised with this application.

5. Clinical Pharmacology

The reader is referred to the reviews of Dr. Kim and the QT TQT team. **PKU-013** was an open-label, randomized, three treatment, six sequence, three-period crossover study in 32 healthy volunteers. The trial assessed the bioavailability of Kuvan® with three different methods and conditions of administration: tablets dissolved in water given in a fasted state; intact tablets given in a fasted state; and intact tablets given in a fed state. Healthy adults between 18 and 50 years inclusive were eligible for participation. Trial participants received Kuvan® 10 mg/kg as a single dose during each treatment period. In summary Kuvan® in intact tablet versus the dissolved tablet offers similar effects on reduction of Phe levels.

Table 2 below represents the comparison of blood Phe concentration in PKU patients who were exposed to the dissolved versus intact tablets. As shown there is similar pharmacodynamics effect of Kuvan® in reducing Phe levels. Dr. Kim notes that "The reduction of blood phenylalanine by Kuvan® is expected to be at least comparable with intact tablets under the consistent administration condition based on higher systemic exposure with intact tablets. It is advisable to administer Kuvan® under consistent manner to avoid a sudden increase in the systemic exposure."

Table 2: Comparison of Blood Phe concentration in PKU Patients: Dissolved vs. Intact Tablets Method of Administration (PKU-008 Safety Population)*

Statistic	Dissolved Tablets (µmol/L)	Intact Tablets (µmol/L)	Percent Change at Switch
N	55	55	55
Mean ± SD)	560 ± 333	504 ± 285	-0.13 ± 1.32
Median	481	483	0.06
(Min,Max)	(b) (4)		
95% CI	(470, 649)	(427, 581)	
Percent Change at Switch P-value	0.3461		

*Only Phe measurements obtained immediately before and after the change in administration method were considered in statistical calculations.

Source: reproduced from Dr. Epps Clinical review

Effect of Kuvan® on QT Interval:

In terms of the effect on the electrocardiogram, Study QTC-001 was a thorough QT study conducted in 56 healthy volunteers. Kuvan® was administered as dissolved tablets in a fed condition at therapeutic and supratherapeutic doses of 20 mg/kg and 100 mg/kg, respectively. The IRT-QT review team noted that there was no significant QT prolongation at the studied doses. A dose-dependent QT shortening was observed, with a maximum mean placebo-adjusted, baseline-corrected QTcI change from baseline of -3.6 and -8.5 ms (lower bound of 90% C.I: -5.3 and -10.6 ms) following Kuvan® doses of 20 mg/kg and 100 mg/kg, respectively. The review team noted that there was no evidence to show that the magnitude of QT shortening observed with the therapeutic dose puts patients at risk for cardiac arrhythmia. The review team did not recommend including QT shortening language in the Warnings and Precautions section of labeling due to the small magnitude of QT shortening observed with the therapeutic dose. I agree with the conclusion that Congenital short QT syndrome is rare disorder and that appropriate language in the Warnings and Precautions section of labeling is not warranted based on the small magnitude of QT shortening. This position has been agreed to by the QTRT.

Clinical pharmacology recommendations for changes to the labeling included the following (see Dr. Kim's review for the specific proposed labeling language):

Section 5: Warnings and Precautions

- Addition of a statement that Kuvan® should not be administered to patients with history and clinical findings suggestive of congenital short QT syndrome.

Section 12.2 Pharmacodynamics

- Description of the thorough QT study and its results, including a statement that the clinical significance of QT shortening in the range observed in the study is not known.

Pharmacokinetics

- Description of the PKU-013 relative bioavailability study.

Addition of information on the metabolic pathway of Kuvan®

6. Clinical Microbiology

Clinical microbiology considerations do not apply to this supplemental application because the product is not an antimicrobial product.

7. Clinical/Statistical-Efficacy

I do concur with the reviews of Drs. Epps and Dimick recommending approval of Supplements 9 and 10 (b) (4)

(b) (4)

(b) (4)

(b) (4)

8. Safety

The reader is referred to the Safety review of Dr. Epps. I will comment on two aspects of the Clinical review for labeling implications. Dr. Epps notes in her review: "As mentioned earlier, the long-term neurological effects of Kuvan® are unknown. The two case reports of behavioral changes (hyperactivity in one patient and hyperactivity and difficulty concentrating in the other patient) that coincided with adverse events (Kuvan® overdose; urinary incontinence) raise the question of a potential behavioral effect of Kuvan®. In light of prior reports of behavioral events in other populations treated with Kuvan®, the current labeling should be updated to note that hyperactivity has been reported for Kuvan®." In terms of the biological basis for this assumption within the brain, the reduced pteridine cofactor 6R-L-erythro-5,6,7,8-tetrahydrobiopterin (BH_4) is absolutely required for the synthesis of the monoamine (MA) neurotransmitters dopamine (DA), norepinephrine, epinephrine (E), and serotonin (5-HT), the novel gaseous neurotransmitter nitric oxide and the production of yet to

be identified 1-O-alkylglycerol-derived lipids.[2] Therefore the concern of hyperactivity unrelated to the phenylalanine dietary intake could be responsible for the post marketing reports related to Kuvan®.

9. Advisory Committee Meeting

During this review cycle, an advisory committee meeting was not convened to discuss the current supplement

10. Pediatrics

No specific issues other than those raised above need to be addressed.

11. Other Relevant Regulatory Issues

A. DSI audits

No DSI inspections were requested because the key clinical study sites were investigated in prior approvals and all studies were of an open-label design.

12. Labeling

I concur with the recommendations made by Dr. Dimick and the team for labeling revisions

(b) (4)

(b) (4)

[2] Kapatos G. The neurobiology of tetrahydrobiopterin biosynthesis: A model for regulation of GTP cyclohydrolase I gene transcription within nigrostriatal dopamine neurons.2013; **IUBMB Life**;Vol 65, Iss. 4, pages 323–333.

(b) (4)

[redacted]

13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action:

All of the review divisions recommended an Approval for Supplements 9 and 10 which gained concurrence from the Clinical reviewer and CDTL. I agree with the recommendations from these disciplines for Approval to supplement the current Kuvan® labeling to include revisions to the label as outlined above.

(b) (4)

[redacted]

(b) (4)

13.2 Risk Benefit Assessment:

I have concluded that the data in these submissions do reflect a risk and benefit similar to the approved Kuvan® for the treatment of BH_4-responsive PKU. The product has a favorable risk/benefit profile**.**

Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies:

There are no requirements for postmarketing risk evaluation and mitigation strategies.

(b) (4)

(b) (4)

FULFILLMENT OF POSTMARKETING COMMITMENTS

Postmarketing commitment #5 is considered fulfilled.

(b) (4)

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

/s/

ANDREW E MULBERG
12/18/2013
Deputy Director Summary Review