CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
22-181

SUMMARY REVIEW

Decisional Review
Kuvan™ (sapropterin) for the Treatment of Phenylketonuria

Date:　　　December 13, 2007

From:　　　Daniel A. Shames MD
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　　　　　　　Director (Actg), Division of Gastroenterology Products (DGP)
　　　　　　　CDER/FDA

To:　　　　File

Identifying Information

NDA #:	22-181
Applicant:	BioMarin Pharmaceutical Inc.
Product name:	Kuvan™ sapropterin dihydrochloride (tetrahydrobiopterin; BH$_4$)
Proposed Trade Name:	Kuvan™
Submission date:	May 25, 2007
Stamp date:	May 25, 2007
PDUFA goal date:	November 25, 2007
Formulation:	Kuvan™ 100 mg Tablets for oral administration
Indication	To reduce blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin-responsive phenylketonuria (PKU). Kuvan™ is to be used in conjunction with a Phe restricted diet.
Proposed regimen:	5 to 20 mg/kg/day orally once daily
Regulatory Decision:	Approval

I consulted the reviews listed below as a basis for my regulatory actions. This communication summarizes the key issues related to the decision to approve this application and its associated labeling and post-marketing commitments. A more detailed summary of these issues can be found in the excellent review of Dr. Anne Pariser who was the cross-discipline team leader (CDTL) for this project. The form and content of my review are based in large part on Dr. Pariser's review. Further in-depth review and analysis of the specific issues can be found in the primary reviews of the listed individuals.

The primary review disciplines have all written high quality review documents for this NDA submission, which should be consulted for more specific details. The primary review documents include the following:

- Clinical Review: Ethan D. Hausman, M.D., dated 07-December-2007.
- Statistical Review and Evaluation, Clinical Studies: Stella Grosser, Ph.D., dated December-2007.
- Pharmacology/Toxicology Review: Fang Cai, Ph.D., dated 27-November-2007.

- Clinical Pharmacology Review: Hae-Young Ahn, Ph.D., dated 29-October-2007.
- Chemistry, Manufacturing and Controls (CMC; Quality) Review: Yichun Sun, Ph.D., dated 19-November-2007.
- Division of Scientific Investigations (DSI) Clinical Inspection Summary: Khairy Malek, M.D., dated 14-November-2007.
- Division of Medication Errors and Technical Support (DMETS) Proprietary Name, Labels and Labeling Review: Denise V. Baugh, Pharm.D., dated 14-November-2007.
- Division of Drug Marketing, Advertising, and Communications (DDMAC): Michael Brony, dated 15-November-2007.
- Interdisciplinary Review Team for QT Studies Consultation: Christine Garnett, Pharm.D., dated 07-November-2007.

1.0 Introduction
Kuvan is a New Molecular Entity (NME) that received Orphan Designation for the treatment of HPA in January, 2004. Kuvan is an immediate-release oral formulation of sapropterin dihydrochloride (sapropterin), a synthetic form of BH_4. BH_4 is an essential cofactor in the hydroxylation of Phe to tyrosine, which is catalyzed by the enzyme phenylalanine hydroxylase (PAH). The proposed mechanism of action for BH_4 in the treatment of PKU is the stimulation of the residual activity of PAH. PAH is altered (mutated) in patients with PKU. This NDA submission was received on 25-May-2007, the application was granted Priority review status, and the PDUFA date was set as 25-November-2007. Kuvan will be the first pharmaceutical treatment for PKU.
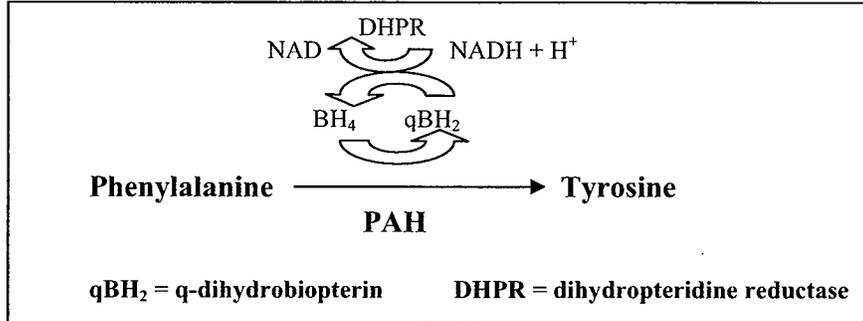
This decisional review contains my summary, assessment and conclusions regarding the major issues found in this original New Drug Application (NDA) for Kuvan™

2.0 Background
PKU is a rare autosomal recessive inherited disorder. Approximately one of every 15,000 infants in the United States (US) is born with PKU. Affected patients have deleterious mutations in the *PAH* gene that lead to deficient hepatic PAH enzymatic activity, which results in elevated levels of blood Phe (hyperphenylalaninemia, HPA). HPA is toxic to the central nervous system (CNS), and prolonged elevations in blood Phe lead to neurocognitive impairment. More than 400 different *PAH* mutations have been identified, and most patients are compound heterozygotes. Consequently, PKU has a broad spectrum of phenotypes.

The hydroxylation of Phe to tyrosine is the first and rate-limiting step in Phe oxidation that eventually results in the complete oxidation of Phe to CO_2 and water. In this reaction, BH_4 binds with PAH and then reacts with oxygen to form an active intermediate that hydroxylates Phe to produce tyrosine. BH_4 is converted to q-dihydrobiopterin (qBH_2) in this reaction. Normally, BH_4 is then recycled by the NADH-dependent enzyme dihydropteridine reductase (DHPR), which converts qBH_2 to active BH_4. The hydroxylation of Phe to tyrosine is represented graphically in the following figure:

*Figure 1: Hydroxylation of Phenylalanine to Tyrosine

$$NAD \longleftarrow \overset{DHPR}{\longrightarrow} NADH + H^+$$

$$BH_4 \qquad qBH_2$$

Phenylalanine $\longrightarrow$ Tyrosine

PAH

qBH_2 = q-dihydrobiopterin   DHPR = dihydropteridine reductase

*Copied from Review of Dr. Anne Pariser, Pg.2

BH_4 also serves as a natural cofactor for the hydroxylation of aromatic amino acids (e.g., tyrosine and tryptophan), and for nitric oxide synthase and glyceryl-ether monooxygenase.

In patients with BH_4-responsive PKU, BH_4 appears to stimulate residual PAH activity, promoting the hydroxylation of Phe to tyrosine, and resulting in lower blood Phe levels; however, no clear association with the type of PAH mutation and BH_4-responsiveness has been found to date.

HPA can also be a consequence of primary BH_4 deficiency. Patients with primary BH_4 deficiency have normal activity of PAH; however, they have mutations in one of several genes coding for the enzymes involved in BH_4 synthesis or recycling, resulting in HPA. Primary BH_4 deficiency is found in about 1% of patients with HPA.

Phe is an essential amino acid that is obtained from the diet. Phe is necessary to meet requirements for endogenous protein synthesis. The nutritional requirement for Phe is difficult to estimate in normal subjects, but estimates in treated PKU patients indicate that the minimum requirement to support protein synthesis is approximately 200 to 500 mg/day in infants and young children, and probably not more than 1.5 times greater than that in older children and adults.

Newborn screening for PKU began in the US in the 1960s, and all states in the US currently screen infants for PKU. Newborn screening has been very successful in preventing severe mental retardation that can result from PKU. When diagnosed early in the newborn period and treated by diet to achieve good metabolic control, infants with PKU have normal health and development.

The National Institutes of Health (NIH) held a Consensus Conference on the screening and management of PKU in October, 2000. Findings and recommendations of the conference were published in 2001.[1] Important findings from this publication that will contribute to understanding of the regulatory decision are as follows:

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[1]National Institutes of Health Consensus Development Panel. National Institutes of Health Consensus Development Conference statement: Phenylketonuria: Screening and management, October 16-18, 2000. Pediatrics 2001;108:972-982.

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- Implementing a Phe-restricted diet early in life can significantly reduce mental deficiencies associated with PKU. Age at treatment initiation and levels of metabolic control have been clearly shown to influence neurocognitive outcomes; patients with poorer metabolic control (i.e., elevated Phe levels) show significantly lower scores on measures of IQ, attention, and reaction time.

- Metabolic control is necessary across the life span of individuals with PKU. Dietary discontinuation before eight years of age is associated with poorer performance on IQ measures. The effects of dietary discontinuation at older ages ($\geq$12 years of age) are less clear. Adults did not show decreasing IQ if they were not on restricted diets; however, these adults manifest poorer performance on measures of attention and speed of processing.

- Infants with blood Phe levels >600 μmol/l (10 mg/dL) should start treatment within a week after birth. Most physicians treat newborns with persistent levels between 420 and 600 μmol/l.

- There is no consensus concerning optimal levels of blood Phe, either across different countries or among treatment centers in the US, and formally recommended guidelines do not exist in the US. The most commonly reported blood Phe recommendations in US clinics are 120 and 360 μmol/l (2 to 6 mg/dL) for neonates through age 12 years, and between 120 and 900 μmol/l (2 to 10 mg/dL) for ages greater than 12 years. The Conference stated that maintenance of Phe levels between 120 and 360 μmol/l (2 to 6 mg/dL) for patients $\leq$12 years of age seems to be medically necessary for ensuring optimal outcome. The Conference strongly encouraged further restricting the recommended range to 120 to 600 μmol/l for patients over 12 years.

The current treatment for HPA due to PKU is to restrict Phe in the diet and to supplement the diet with low-Phe medical foods. Compliance with diet, especially in older children, adolescents, and adults, is difficult, and non-compliance at older ages is almost universal. Barriers to adherence include economic, psychosocial, and health care system issues. Thus, new treatments for PKU are clearly needed.

BioMarin's initial Investigational New Drug (IND) application for the sapropterin clinical development program for the treatment of PKU was opened on 16-August-2004, under IND #69,708. Prior to the opening of this IND in 2004, sapropterin dihydrochloride (tetrahydrobiopten; BH$_4$) as Biopten 2.5% granules was approved for use in Japan in 1992 for the treatment of atypical HPA due to primary BH$_4$ deficiency due to mutations in GTP cyclohydrolase 1,6-pyruvoyl-tetrahydropterin synthase or dihydropteridine reductase (DHPR) (licensed by Daiichi Suntory Pharm Co [Daiichi Suntory]). The labeled dosage for the treatment of primary BH$_4$ deficiency is 2 to 5 mg/kg/day (of sapropterin) orally in one to three divided doses. BioMarin acquired the rights to sapropterin from Daiichi Suntory to develop and commercialize sapropterin in countries outside of Japan.

An End-of-Phase 2 (EOP2) meeting was held between the Division of Metabolic and Endocrine Products (DMEP) and BioMarin on 22-November-2004. At this meeting,

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DMEP agreed that blood Phe levels would be an acceptable primary endpoint in clinical studies submitted in the NDA; however, the Applicant was requested to also submit a plan for post-approval follow-up of treated patients to assess long-term potential benefits of treatment (e.g., long-term clinical endpoints such IQ and neuropsychological status).

3.0 CMC Issues
The Drug Substance (DS) used in Kuvan is sapropterin dihydrochloride, a synthetic form of the naturally occurring tetrahydrobiopterin. Sapropterin dihydrochloride DS is produced through ▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄
▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄ The DS is manufactured at two manufacturing sites: ▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄
▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄, and sapropterin dihydrochloride DS manufactured at all manufacturing sites has been demonstrated to be comparable.

The Drug Product (DP) Kuvan (sapropterin dihydrochloride) is round, off-white to light yellow immediate-release tablets. The to-be-marketed-product (TBMP) for Kuvan will be 100 mg tablets manufactured at Lyne Laboratories, Inc. in Brockton, MA (debossed with "177"). Tablets are manufactured by ▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄
active pharmaceutical ingredient (API) and excipients.

Several changes were made to the TBMP (formulation B) from the tablets used in Phase 3 clinical studies (formulation A).

The CMC Reviewer commented that although the different tablet formulations were comparable by the properties evaluated (e.g., dissolution profiling), the impact of the manufacturing changes on the clinical performance of the DP is not clear if whole tablets are taken orally, considering the number and degree of changes made, most importantly the change in manufacturing process from ▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄▄
However, when the tablets used in the clinical studies (formulation A) were administered during the clinical studies, they were dissolved in liquids (such as water and apple juice), which diminished the differences between the manufacturing processes. It was concluded (see section 5.0) that although clinical comparability between the formulations had not been established, there is no need to link the tablets used in clinical studies (formulation A) and the TBMP (formulation B) if the tablets will be dissolved in dosing liquids before being taken. Therefore, Kuvan tablets should be labeled for administration to patients only after dissolution in water or apple juice, and not as intact tablets.

The overall assessment based on the review of the CMC data submitted in this NDA is that the application should be approved

4.0 Nonclinical Pharmacology/Toxicology
Significant findings from the Pharmacology/Toxicology review that required placement in the prescibers labeling are summarized below. **Reference to section number in prescribers labeling is bolded.**
- Sapropterin tested positive in the bacterial reverse mutation and chromosome aberration test, but was not mutagenic when assessed in the mouse micronucleus tests. Sapropterin may have mutagenic and/or clastogenic potential.
  o **13. NONCLINICAL TOXICOLOGY**

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- The carcinogenic potential of sapropterin was assessed in a 104-week oral carcinogenicity study in rats, and in a 78-week oral carcinogenicity study in mice. ▬▬▬▬▬▬ increase in the incidence of benign adrenal pheochromocytoma in males, which was significantly increased in high-dose (250 mg/kg/day) male rats relative to the control group. ▬▬▬▬▬

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  - ○ 13. NONCLINICAL TOXICOLOGY

- Because of positive findings in some pre-clinical fetal developmental studies a Pregnancy Category C was recommended.
  - ○ 8.1 PREGNANCY

- Sapropterin is excreted in the milk of intravenously, but not orally treated lactating rats. It is not known whether sapropterin is excreted in human milk. The Pharmacotoxicology Reviewer recommended that labeling include wording that because of the potential for serious adverse reactions in nursing infants from sapropterin, and because of the potential for tumorigenicity shown for sapropterin in the rat carcinogenicity study, a decision should be made whether to discontinue the drug taking into account the importance of the drug to the mother.
  - ○ 8.3 NURSING MOTHERS

The overall assessment based on the review of the Pharmacotoxicology data submitted in this NDA is that the application should be approved.

5.0 Clinical Pharmacology/ Biopharmaceutics
Important issues and **bolded references to sections in prescriber label follows**:

- Patients who required concomitant treatment with any drug known to inhibit folate synthesis (e.g., methotrexate) were excluded from study. Folate synthesis inhibitors are known to inhibit DHPR *in vivo* and *in vitro*. After conversion of BH_4 to qBH_2 during the hydroxylation of Phe to tyrosine, BH_4 is normally recycled back to active BH_4 by DHPR (see figure 1). Thus, folate synthesis inhibitors have the potential to decrease levels of BH_4.
  - ○ **5.6 Use With Caution When Co-administering Kuvan and Medications Know to Inhibit Folate Metabolism**

- Mean blood Phe levels remained stable over the course of the 24-hour period after administration of Kuvan 10 mg/kg/ once per day. Intra-subject variations in blood Phe levels were relatively small, and there seemed to be no spikes of Phe levels in individual data. Thus, the once-daily dosing interval of Kuvan is based on the pharmacodynamic (PD) properties of sapropterin on blood Phe reduction, rather than the known pharmacokinetic (PK) properties (T_{max} and $T_{1/2}$, each 4 hours for oral administration). It is noted that all of the PKU clinical efficacy and safety studies conducted in the Kuvan clinical development program were conducted using a once daily dose of Kuvan.
  - ○ **2.1 Dosage**

- As previously mentioned, the Kuvan tablets used in the clinpharm studies were manufactured ▬▬▬▬▬ (formulation A), and the TBMP is produced by ▬▬▬ (formulation B). ▬▬▬▬▬

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  ▬▬▬▬ However, the Clinical Pharmacology Reviewer recommended that Kuvan tablets be labeled for administration to patients only after dissolution in water or apple juice, and not as intact tablets, since dissolution in solution of the tablet diminished the differences between the formulations manufactured by different processes.
  - **2.2 Administration**

- Since orange juice, which was used in the clinical trials along with water and apple juice to dissolve the Kuvan tablet, contains a significant amount of Phe, the Applicant proposed that the drug be dissolved in water or apple juice when marketed. The bioavailability (BA) of Kuvan dissolved in water was studied, however, the BA of Kuvan dissolved in apple juice was not studied. The stability data on Kuvan dissolved in apple juice and water were comparable (per CMC Reviewer). Therefore, the Clinical Pharmacology Reviewer assessed that the Applicant's proposal that Kuvan be administered dissolved in water or apple juice is acceptable.
  - **2.2 Administration**

- Food effect studies indicated that food (high fat, high calorie meals) increased the BA of Kuvan, especially when the drug was administered as solution dissolved in water (an 87% increase compared to fasting conditions). Therefore, the Clin Pharm reviewer recommended that the drug be taken with food in order to optimize the bioavailability of Kuvan.
  - **2.1 Dosage**

- ▬▬▬▬▬ the starting dose of Kuvan be 20 mg/kg/day, based on the results of Study PKU-006 (see section 6.0 of this review), and that doses of Kuvan may be adjusted in the range of 5 to 20 mg/kg/day. However, a starting dose of 10 mg/kg/day was used in Study PKU-001 (n=490), with an approximately 20% response rate seen in this study. Thus, the 10 mg/kg/day dose has been demonstrated to be efficacious as a starting dose, and sapropterin 10 mg/kg/day is recommended as the starting dose. Patients may then be titrated up or down from the 10 mg/kg/day dose based on response.
  - **2.1 Dosage**

- A clear dose-response relationship with Kuvan was demonstrated during the forced dose-titration period in Study PKU-004 (see section 6.0 of this review). Efficacy was observed in this clinical study in some patients with doses as low as 5 mg/kg/day. The highest dose administered in clinical studies was 20 mg/kg/day, which demonstrated acceptable results. Thus, a dose range of 5 to 20 mg/kg/day is acceptable.
  - **2.1 Dosage**

The overall conclusion is that the clinical pharmacology and biopharmaceutics information submitted to NDA 22-181 were acceptable.

6.0 Clinical/Statistical Efficacy

The most important clinical efficacy information submitted in the NDA is from four BioMarin-sponsored, short-term (up to 30 weeks) clinical studies conducted with Kuvan (sapropterin) in a total of 579 patients with PKU. The data contained in these four studies were amenable to substantive review, and are supportive of the clinical effectiveness of Kuvan in the treatment of BH_4-responsive PKU. In all four studies, sapropterin (or placebo) was administered as a single daily dose with the tablets dissolved in water, apple juice, or orange juice. Diet was controlled only in the PKU-006 study. In the remaining studies (PKU-001, -003, and -004), patients were instructed not to alter their diet and dietary Phe intake was monitored by patient-reported diaries, but no formal diet-control measures were undertaken during these studies. These four studies and their efficacy results are described below:

PKU-001 (Enrichment Study) was a non-randomized, open-label (OL), uncontrolled, safety and efficacy study of sapropterin 10 mg/kg/day administered once a day for up to eight days to 489 patients with PKU, ages eight years and older who were not under dietary-control with a Phe-restricted diet at study entry. The purpose of the study was to identify "responders" to sapropterin treatment, defined as patients who had a $\geq$30% decrease in blood Phe from Baseline (pre-treatment) at Day 8. Responders were then eligible for enrollment in PKU-003 (Efficacy Study).

The results for PKU-001 demonstrated that 20% of patients with PKU, ages eight years and older, were identified as responders to treatment with sapropterin 10 mg/kg/day. Responders were eligible for entry into PKU-003. Non-responders were discontinued from treatment with sapropterin.

PKU-003 (Efficacy Study) was a randomized (1:1, sapropterin or placebo), double-blind (DB), placebo-controlled (PC), safety and efficacy study of sapropterin 10 mg/kg/day administered once a day for six weeks to 89 patients with PKU, who were responders in PKU-001. The primary efficacy endpoint was mean change in blood Phe from Baseline (pre-treatment) at Week 6 in each treatment group.

The sapropterin-treated group had a mean change in blood Phe from Baseline at Week 6 of -239 µmol/l (SE 38), and the placebo-treated group had a mean change of 6 µmol/l (SE 36). The difference in mean change from Baseline between the two groups was significant (p<0.001) in favor of sapropterin.

For the secondary endpoint of difference in mean blood Phe levels between the treatment groups from Baseline at the weekly visits (Week 1, 2, 4, and 6), a separation between the groups (non-overlapping CI) is seen at the end of the first week of treatment (Week 1) that is sustained through Week 6. The results are displayed graphically in the following figure (*electronically copied and reproduced from the Applicant's submission; phenoptin = sapropterin).

*Figure 2: PKU-003, Mean Blood Phe Levels over Time
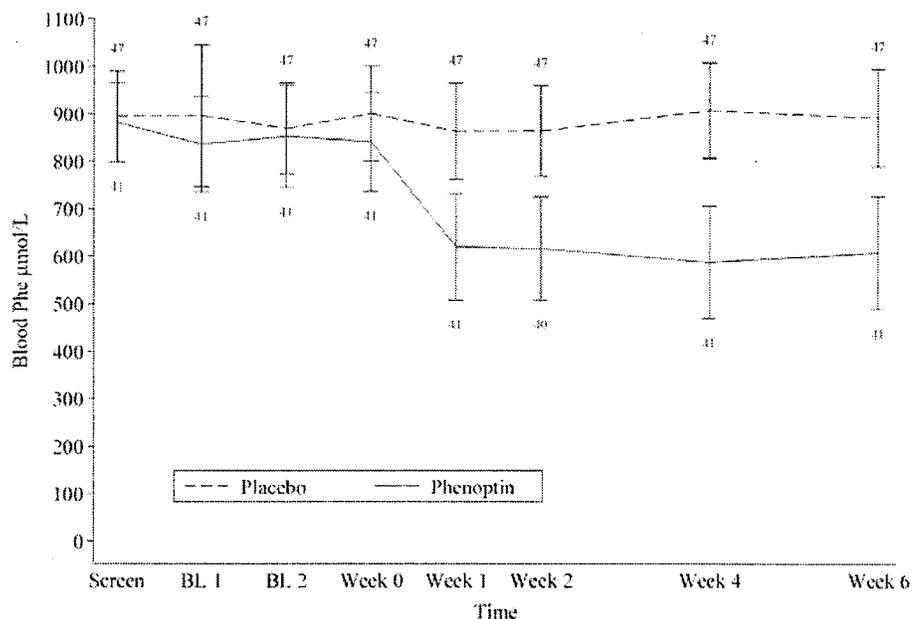
For the secondary endpoint of proportion of patients in each treatment group who had a blood Phe level <600 μmol/l at Week 6, 54% of sapropterin-treated patients and 23% of placebo-treated patients had a Week 6 blood Phe level <600 μmol/l (p=0.004).

The results for PKU-003 demonstrate a significant decrease in blood Phe levels with sapropterin treatment as compared to placebo treatment in patients with BH$_4$-responsive PKU. The pharmacodynamic (PD) effect of sapropterin treatment was evident after one week of treatment (first measurement of blood Phe level during DB treatment), and was sustained throughout the six-week treatment period of the study.

PKU-004 (Extension Study) was an OL, uncontrolled, extension study of 80 patients who completed PKU-003. The total duration of sapropterin treatment in PKU-004 was 22 weeks. PKU-004 was conducted in two parts:

Part 1 was a six-week, OL, forced dose-titration period in which patients were consecutively treated with three different doses of sapropterin (5, then 20, then 10 mg/kg/day) for two weeks at each dosage level. The objective of Part 1 was to evaluate the dose-response of three different dosage levels of sapropterin. After completion of the forced dose-titration period, patients were then maintained on sapropterin 10 mg/kg/day for an additional four weeks (Week 6 to Week 10) while each patient's optimal dose of sapropterin was determined from the forced dose-titration period (with the objective of maintaining blood Phe level <600 μmol/l, or a maximum dose of 20 mg/kg/day).

For each pairwise comparison of the dose groups, the mean change in blood Phe level differed significantly: the difference between the 5 vs. 10 mg/kg/day and between the 5 vs. 20 was statistically significant at p<0.0001, and between the 10 vs. 20 mg/kg/day was statistically significant at p=0.0085. The results are summarized in the following table.

**Table 1: PKU-004, Forced Dose-Titration Period Blood Phe Level Results

Sapropterin Dose	Patients, n =	Mean (SD) Blood Phe Level, µmol/l (SD)	Mean Change (SD) in Blood Phe Level from Week 0, µmol/l (SD)
Week 0*	80	844 (398)	-
5 mg/kg/day	80	744 (384)	-100 (295)
10 mg/kg/day	80	640 (382)	-204 (303)
20 mg/kg/day	80	581 (399)	-263 (318)

*No treatment,**copied from the review of Dr. Anne Pariser

The mean blood Phe level remained essentially unchanged from Week 6 to Week 10 while all patients were receiving sapropterin 10 mg/kg/day.

Part 2 was a 12-week, OL, fixed-dose treatment period, in which each patient's daily sapropterin dose was 5, 10, or 20 mg/kg/day based on the patient's blood Phe level results from Part 1. The objective of Part 2 was to evaluate the longer-term (12-week) safety and efficacy of sapropterin.

The results for Part 2 demonstrate that patients received sapropterin at a dose of 5 mg/kg/day (6 patients), 10 mg/kg/day (37 patients), and 20 mg/kg/day (37 patients) for Week 10 through Week 22. On average, patients maintained blood Phe levels ranging between approximately 620 and 650 µmol/l during this time.

The overall results for PKU-004 indicate a clear dose-response effect of sapropterin on blood Phe levels in patients with BH_4-responsive PKU, with statistically significant differences in mean change in blood Phe levels observed between the different dosage levels (5, 10, and 20 mg/kg/day). The results also show that the effect of sapropterin treatment on blood Phe levels was sustained throughout the 22-week treatment period of the study.

PKU-006 (Diet Study) was conducted in two parts:
Part 1 was a non-randomized, OL, uncontrolled, safety and efficacy treatment period in which 90 patients with PKU, ages four to 12 years, who were under dietary-control with a Phe-restricted diet at study entry, were administered sapropterin 20 mg/kg/day for up to eight days. The purpose of Part 1 was to identify responders to sapropterin treatment (defined as patients who had a ≥30% decrease in blood Phe from Baseline at Day 8) for continuation in Part 2 of the study.

In Part 1 of the Study 006, 56% of patients with PKU, were identified as responders to treatment with sapropterin 20 mg/kg/day. Responders were eligible for entry into Part 2 of PKU-006. Non-responders were discontinued from treatment with sapropterin.

Part 2 was a randomized (3:1, sapropterin or placebo), DB, PC, dietary Phe-supplementation, safety and efficacy treatment period in which 45 responders from Part 1 were randomized to DB study drug treatment (sapropterin n= 33, placebo n=12). Patients received sapropterin 20 mg/kg/day without dietary Phe supplementation from Week 0 (entry into Part 2) to Week 3. Beginning at Week 3, all patients' dietary Phe intake was supplemented by 5 mg/kg/day for two weeks. Dietary Phe supplementation could then be adjusted at Weeks 5, 7, and 9 based on blood Phe level results at Weeks 4, 6, and 8, while maintaining blood Phe control (i.e., blood Phe <360 µmol/l). The primary endpoint for

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Part 2 (and for PKU-006) was the mean amount of dietary Phe supplement tolerated after ten weeks of DB treatment in each treatment group.

In this part of Study 006, the sapropterin group tolerated a mean dietary Phe supplement of 21 mg/kg/day at Week 10, which was significantly different for the pre-treatment amount of zero supplement (p<0.001). This amount was also significantly greater than amount tolerated by the placebo group of 3 mg/kg/day. The sapropterin group also had a significant mean decrease in blood Phe from Week 0 (pre-treatment) to Week 3 (prior to dietary supplement) of 149 μmol/l.

7.0 Safety
The most commonly reported AEs in sapropterin-treated patients were headache (11 of 74 patients; 15%), upper respiratory infection (URI; 12%), rhinorrhea (11%), pharyngolaryngeal pain (10%), and diarrhea and vomiting (8% each). The most commonly reported AEs (reported by ≥4% of patients) are summarized in the following table.

Table 2: Most Common (≥4% of patients) AEs Reported in DB, PC Clinical Studies

| | Double-Blind Treatment | |
	Sapropterin	Placebo
Safety Population, n =	74	59
Patients experiencing any AE, n (%)	47 (64)	42 (71)
Adverse Events Preferred Term*	n (%)	n (%)
Headache	11 (15)	8 (14)
URI	9 (12)	14 (24)
Rhinorrhea	8 (11)	0
Pharyngolaryngeal pain	7 (10)	1 (2)
Diarrhea	6 (8)	3 (5)
Vomiting	6 (8)	4 (7)
Cough	5 (7)	3 (5)
Pyrexia	5 (7)	4 (7)
Abdominal pain	4 (5)	5 (8)
Contusion	4 (5)	1 (2)
Rash	4 (5)	4 (7)
Nasal Congestion	3 (4)	0

*MedDRA Coding **copied from review of Dr. Anne Pariser

AEs reported during open-label, uncontrolled sapropterin administration tended to be similar in types and frequencies to the AEs reported during the DB, PC trials, and no additional safety signals were noted during longer-term (up to 30 weeks) administration of sapropterin.

However, there are two potential serious safety issues which need to be addressed separately. They are neutropenia and QT prolongation.

Neutropenia, defined as an absolute neutrophil count (ANC) less than the lower limit of normal (LLN) was noted to be temporally associated with sapropterin use in 24 of the 579 patients (4%) exposed to sapropterin. No infections or other sequelae were noted in these patients, and most patients recovered either with continued sapropterin treatment or after sapropterin administration was stopped (no patient was specifically withdrawn from sapropterin treatment due to a low ANC). Since most of these patients were exposed to

sapropterin in OL, uncontrolled studies, and challenge-dechallenge-rechallenge information was not available, a definitive association of neutropenia with sapropterin use could not be established; however, the development of neutropenia will be noted in the **Adverse Reactions** section of the product labeling.

A consultation from the QT-Interdisciplinary Review Team (QT-IRT) was requested by the Division during the review cycle. The consultation was requested because sapropterin is a new molecular entity (NME), and a clinical cardiac safety evaluation was not performed as part of the clinical development program for sapropterin in the treatment of PKU. Specifically, no routine electrocardiograph (ECG) monitoring was performed as part of the safety procedures in the clinical studies in PKU patients, and a thorough QT (TQT) study has not been performed. It should be noted that *in vitro* (hERG) and cardiovascular dog studies were negative and no signal arose in any of the clinical studies. However, no clinical study was designed appropriately to detect a QT prolongation. Since sapropterin is a new drug with systemic bioavailability, the QT-IRT recommended that sapropterin undergo clinical ECG evaluation. Therefore, the performance of a TQT study with sapropterin will be required of the Applicant as a condition of approval (i.e., as a post-marketing commitment, PMC).

Sapropterin appeared to be well-tolerated by patients with PKU during clinical trials. No deaths were reported, and few serious or clinically significant safety findings were noted. Common AEs reported during DB clinical trials included headache, URI, rhinorrhea, pharyngolaryngeal pain, diarrhea, and vomiting, which occurred with similar frequencies in sapropterin- and placebo-treated, groups, tended to be mild to moderate in intensity, and tended to resolve without intervention.

<u>8.0 Advisory Committee Meeting</u>
NDA 22-181 was not referred to an advisory committee for review for the following reasons: The efficacy endpoints were clear and easily measured. The evaluation of safety did not reveal any concerning safety signals with Kuvan administration, and the design and results of the efficacy trials did not pose particular concerns. Kuvan did not have any controversial issues which would have benefited from advisory committee discussion.

<u>9.0 Labeling</u>
For efficacy, labeling will identify (in section 14 of the **CLINICAL STUDIES** section of the prescriber label) the results of the short-term (up to 30 weeks) clinical efficacy and safety studies conducted in patients with PKU, ages four years and older, that show evidence of the effectiveness of Kuvan in lowering blood Phe levels in a subgroup group of patients with PKU.

For safety, the **Warnings and Precautions** section of the labeling will reflect that:
- The long-term effects of Kuvan treatment on neurocognitive outcome in patients with PKU have not been determined.
- Not all patients respond to Kuvan.
- Dietary control with a Phe-restricted diet and close monitoring of blood Phe levels by medical professionals familiar with the treatment of PKU are necessary for all patients receiving treatment with Kuvan.

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- Kuvan should be used with caution in patients with hepatic insufficiency, and with co-administration of drugs known to inhibit folate metabolism, drugs known to affect nitric oxide-mediated vasorelaxation, and with levodopa.

Labeling will also state that patients with PKU who are less than four years of age have not been studied in clinical trials with Kuvan (in section **8.4, the Pediatric Use,** section of the prescriber label.)

10 Conclusions and Recommendations
10.1 Efficacy conclusions
I agree with the assessment of the efficacy findings by the CDTL and Primary Reviewers that the design and analysis of the studies are adequate, and the data provide substantial evidence to conclude that Kuvan is efficacious in lowering blood Phe levels in selected PKU patients.

10.2 Safety conclusions
Sapropterin appears to be well-tolerated by patients with PKU, with few serious or clinically significant safety findings reported during clinical trials. The Division will request that a TQT study with sapropterin be conducted in normal volunteers. The study should be designed per ICH E14 recommendations, e.g., as a single-dose, positive- and placebo-controlled, cross-over study in normals volunteers. I agree with the review team that the TQT study can be conducted in the post-approval period, and will be required as a condition of approval as a post-marketing commitment (PMC). The post-approval conduct of the TQT study can be justified based on the facts that: 1) no noteworthy cardiac or other safety signal has been identified to date in clinical·studies for PKU or in the clinical experience with other disease indications, such as hypertension; 2) PKU patients are not at higher-risk of cardiovascular problems than the non-PKU population; and 3) sapropterin appears to have a favorable risk-benefit profile in BH_4-responsive PKU patients, and appears to address an unmet medical need. Thus, delaying approval to conduct the TQT study does not appear to be warranted

10.3 Risk Benefit Assessment
Kuvan was well-tolerated by patients, with few serious or clinically significant safety findings reported during clinical safety (and efficacy) studies conducted in patients with PKU. Given the potential benefits of Kuvan administration to patients with BH_4-responsive PKU, I believe that Kuvan has a favorable risk-benefit profile based on the information in the submitted application.

10.4 Post-Marketing Commitments
BioMarin has agreed to a number of Post-Marketing Commitments (PMCs) for Kuvan that are needed to adequately define the safety and appropriate use of Kuvan post-approval. These PMCs are:

1. BioMarin commits to designing and implementing a safety, efficacy, and pharmacokinetics study with Kuvan (sapropterin dihydrochloride) in patients with PKU who are four years of age or younger at study entry. Efficacy is to be assessed by the pharmacodynamic outcome measure of blood phenylalanine levels over a six-

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month period of treatment. A study protocol will be submitted to CDER by June 14, 2008, for concurrence, and the study will be initiated by December 14, 2008. The final study report for this study will be submitted to CDER by June 14, 2010.

2. BioMarin commits to designing and implementing a long-term study designed to assess growth and neurocognitive development with treatment with Kuvan (sapropterin dihydrochloride) in patients who are eight years of age or younger at study entry. This study is to include blinded assessments of growth (including standardized measurements of recumbent length or height, weight, and head circumference), and developmental testing (the scales used need to be prospectively agreed upon) at six- to twelve-month intervals over a seven-year period. A study protocol will be submitted to CDER by June 14, 2008, for concurrence, and the study will be initiated by December 14, 2008. The final study report for this study will be submitted to CDER by June 14, 2017.

3. BioMarin commits to completing the open-label extension study PKU-008, entitled "A Phase 3b, Multicenter, Open–Label Extension Study of Phenoptin™ in Subjects with Phenylketonuria Who Participated in Studies PKU–004 or PKU–006".[2] Patients who participated in the extension study PKU-004 will be treated under PKU-008 for a minimum of two years of total treatment with Kuvan (sapropterin dihydrochloride). Patient accrual is complete, the two-year cutoff period is to be completed on May 30, 2008, and an interim study report will be submitted to CDER by September 30, 2008. The study is to be completed by September 30, 2009, and a final study report will be submitted to CDER by March 30, 2010.

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

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

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

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

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

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

10.5 Regulatory Action
I agree with the CDTL and the primary reviewers that data in this NDA support the approval of Kuvan for the treatment of HPA due to BH_4-responsive PKU at a dosage of 5 to 20 mg/kg/day administered once daily. These data also provide sufficient information necessary for appropriate product labeling.

**Appears This Way
On Original**

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/s/

Daniel A. Shames
12/13/2007 09:51:15 AM
MEDICAL OFFICER