May 13, 2014

Re: Long-Term Efficacy of KUVAN® (Sapropterin Dihydrochloride) Tablets

Dear Ms. Pallone,

This letter is provided in response to your unsolicited request for information regarding the long-term efficacy of KUVAN® (sapropterin dihydrochloride) Tablets for its indication to lower blood phenylalanine level in patients with hyperphenylalaninemia due to tetrahydrobiopterin responsive phenylketonuria. We are pleased to provide you the following information.

BioMarin Pharmaceutical Inc. does not recommend the use of its products in a manner inconsistent with approved product labeling. This letter and its attachments are provided as informational pieces and should not be viewed as a substitute for good clinical judgment. Please review the attached Kuvan full prescribing information for specifics relating to dosing and special precautions.

Although we attempt to provide a complete and recent review of the literature, the reference citations may not represent a comprehensive list of available information on the subject of your inquiry.

Clinical Experience

The safety and efficacy of Kuvan were evaluated in 6 clinical studies of patients with phenylketonuria (PKU) ranging in age from 1 month to 50 years.[1] Six hundred and forty four (644) patients with PKU (aged 1 month to 49 years) received Kuvan (5 to 20 mg/kg/day) in trials ranging in length from 1 to 164 weeks. The most common adverse events (AEs; ≥4% of patients) were headache, rhinorrhea, pharyngolaryngeal pain, diarrhea, vomiting, cough, and nasal congestion. Long-term safety (mean exposure 659 ± 221 days; maximum 953 days) has been studied in 111 patients aged 4-50 years, receiving Kuvan in doses ranging from 5 to 20 mg/kg per day. Adverse events were similar in type and frequency to those reported in the previous clinical studies. These studies are outlined in Table 1.

Phase 2 Study

PKU-001: A Phase 2, open-label screening study involving 489 patients with PKU was performed to assess the impact of Kuvan treatment on blood phenylalanine (Phe) levels.[2] None of the patients were following a Phe-restricted diet. Patients were considered to be responders to Kuvan if a ≥30% decrease in baseline Phe level occurred within the 8-day study period. Twenty percent of patients responded to Kuvan therapy, with a mean decrease in Phe level of 391.8 µmol/L (± 185.3). Baseline Phe level was not observed to be a predictor of responsiveness to Kuvan. In this study, the most commonly reported AEs (≥5%) included headache, abdominal pain and diarrhea.

Table 1. Summary of Kuvan Clinical Trials[1]

	PKU-001 (n=489)	**PKU-003** (n=88)	**PKU-004** (n=80)	**PKU-006** (n=90)	**PKU-015** (n=93)	**PKU-008** (n=111)
Design	Phase 2, multicenter, open-label, uncontrolled clinical trial	Phase 3, multicenter, double-blind, placebo-controlled study of patients who responded to Kuvan in PKU-001	Multicenter, open-label, extension study of patients who responded to Kuvan in PKU-001 and -003	Phase 3, multicenter study of pediatric patients with PKU	Open-label, single-arm, multicenter trial of pediatric patients with PKU	Long-term, open-label extension study
Age	8-48 years	8-49 years	> 5 years	4-12 years	1 month to 6 years	4-50 years
Dose	10 mg/kg/day x 8 days[a]	Placebo (n=47) or Kuvan 10 mg/kg/day (n=41) x 6 weeks	Dose titration: 5 mg/kg/day x 2 weeks, 20 mg/kg/day x 2 weeks, then 10 mg/kg/day x 2 weeks	20 mg/kg/day x 8 days in combination with a Phe-restricted diet	20 mg/kg/day in combination with a Phe-restricted diet	5-20 mg/kg/day

[a]≥30% decrease in blood Phe from baseline was used in all studies as a marker of response to Kuvan

Phase 3 and Extension Studies

PKU-003: Patients identified as responders to Kuvan in PKU-001 were able to participate in a follow-up, double-blind, placebo-controlled, Phase 3 Study.[3] The primary efficacy endpoint was change from baseline in blood Phe, with secondary endpoints focused on safety outcomes. In addition to being Kuvan responsive, a blood Phe level of ≥600 μmol/L, which was eventually lowered to ≥450 μmol/L following a protocol amendment, was required. The patients, all of whom had relaxed or abandoned a Phe-restricted diet, were randomized to receive either Kuvan 10 mg/kg/day (n=41) or placebo (n=47) for 6 weeks. After 1 week of treatment, patients receiving Kuvan exhibited a mean reduction in blood Phe level of 200 μmol/L, an effect that was maintained for the duration of the study.[3] By Week 6, patients treated with Kuvan had a mean decrease in blood Phe level of 235.9 μmol/L (±257.0) as compared to a decrease of 2.9 μmol/L (±239.5) in placebo-treated patients ($p<0.0001$). Of the 44 Kuvan-treated patients on whom follow-up data were available, 44% had a reduction in blood Phe level of at least 30% as compared with 9% (4/47) in the placebo group. Furthermore, 13 Kuvan-treated patients exhibited a ≥50% decrease in blood Phe level as compared to only 1 placebo-treated patient. Adverse events potentially related to drug treatment were reported for 23% and 20% of patients treated with Kuvan and placebo, respectively, with upper respiratory tract infections, headache, vomiting, abdominal pain, diarrhea, pyrexia, and back pain being the most commonly-reported AEs.

PKU-004: The long-term efficacy and safety of Kuvan therapy were further evaluated in a 22-week, open-label extension study.[4] This was a three-part study including a 6-week forced dose-titration phase, followed by a 4-week dose-analysis phase, and ending with a 12-week fixed-dose phase. During the dose-titration phase, all patients received 5, 20, and 10 mg/kg/day of Kuvan; patients received 10 mg/kg/day of Kuvan in the dose-analysis phase. During the last phase of the study, doses were determined by the patient's blood Phe levels during the dose-titration phase. As with previous studies, reduction in Phe from baseline was the primary efficacy variable. Safety outcomes were also assessed.

Eighty patients were enrolled, with 79 of them completing the entire 22-week study period. A relative dose response to Kuvan therapy was observed during the titration phase, with blood Phe levels decreasing from a mean of 844.0 μmol/L (±398.0) at baseline to 743.9 μmol/L (±384.4), 639.9 (±381.8), and 580.8 μmol/L (±398.8) at Kuvan doses of 5, 10 and 20 mg/kg, respectively.[4] The reductions associated with the 10 and 20 mg/kg/day doses of Kuvan were both statistically significant. After the dose analysis phase, this value was 645.2 μmol/L (±393.4).

During the fixed-dose phase, 6 patients were treated with 5 mg/kg/day of Kuvan, with 37 patients each receiving doses of 10 and 20 mg/kg/day.[4] Overall, the mean change in blood Phe level at 22 weeks compared with the level at baseline was -190.537 μmol/L (±355.7). By the end of the fixed-dose period, 46% of patients (n=36) achieved decreases in blood Phe level of at least 30%.

Of the 80 patients in the study, 68 had at least one AE, all of which, except for one, were graded as mild or moderate in severity.[4] The most commonly reported AEs (≥10%) were headache, pharyngo-laryngeal pain, nasopharyngitis, vomiting, diarrhea, and upper respiratory tract infection. No discontinuations occurred as a result of an AE.

PKU-006: This two-part, double-blind, placebo-controlled study assessed Kuvan use in patients aged 4-12 years who were on Phe-restricted diets with blood Phe levels ≤480 µmol/L at screening.[1,5] All patients were treated with 20 mg/kg/day of Kuvan over an 8-day period to assess responsiveness to therapy. By Day 9, 50 patients (56%) had a ≥30% decrease in blood Phe.

After a washout period, patients were randomized (3:1) to receive either 20 mg/kg/day of Kuvan or placebo for an additional 10 weeks, while maintaining a stable, Phe-restricted diet.[5] Randomization was stratified based on blood Phe values collected during the previous 6 months (<300 or ≥300 µmol/L). After 3 weeks of therapy, a dietary Phe supplement was added every two weeks as long as Phe concentrations remained below 360 µmol/L. The endpoint for this second phase was the daily Phe supplement tolerated as compared to baseline.

At Week 10, the mean daily Phe supplement tolerated by the Kuvan-treated group increased from none at baseline to 20.9 mg/kg (± 15.4) (p<0.001), while placebo-treated patients only tolerated an additional 2.9 mg/kg (± 4.0).[5] The mean difference in Phe supplementation between the Kuvan-treated and placebo-treated cohorts was 17.7 mg/kg (± 4.5, p<0.001). No severe or serious drug-related AEs were reported by either treatment group. The most commonly reported AEs (>10%) in the Kuvan group included rhinorrhea, headache, cough, pharyngo-laryngeal pain, diarrhea, and vomiting.

PKU-015: An open-label, single arm study evaluated the efficacy of Kuvan in 93 patients with PKU aged 1 month to 6 years, of whom, 65 were responsive to Kuvan and participated.[1,6] Adverse reactions in these patients were similar in frequency and type as those seen in other Kuvan clinical trials except for an increased incidence of low Phe levels. After 4 weeks of treatment with Kuvan at 20 mg/kg/day, 57 patients (61%) were identified as responders (defined as ≥30% decreased in blood Phe from baseline) and were subsequently treated for 6 months with Kuvan in combination with a Phe-restricted diet. The efficacy of Kuvan alone on the reduction of blood Phe levels past 4 weeks could not be determined due to the concomitant changes in dietary Phe intake allowed during the study to maintain Phe within protocol-defined target range (120-240 µmol/L).

PKU-008: Patients completing either PKU-004 or PKU-006 were allowed to participate in an additional 36-month extension trial.[7] Enrolling 111 patients, this open-label Phase 3b study was designed to evaluate the long-term safety of Kuvan in known responders. The mean (± SD) exposure to sapropterin for the entire study population was 659 ± 221 days (maximum 953 days). Each patient received Kuvan 5 to 20 mg/kg daily depending on the optimized dose determined in previous trials; there were no dietary restrictions. Although there were no pre-specified efficacy analyses as part of the study design, blood Phe samples were collected.

The median daily dose of Kuvan administered during the trial period was 18.4 mg/kg/day (range, 4.8-22.1 mg/kg/day), with treatment duration lasting from 56 to 953 days.[1,7] Approximately half of patients began the study with Phe levels that were above the recommended treatment guidelines. After the initiation of Kuvan treatment, Phe levels in these patients shifted to within range for the duration of the study. Most AEs reported during the 3-year trial were consistent with previous studies with Kuvan and were mild to moderate in severity. The most common AEs

determined to be related to Kuvan therapy were viral gastroenteritis, vomiting, and headache, each at a frequency of 4.5%. Fifty-five patients received Kuvan both as dissolved and intact tablets. There were no notable differences in the incidence or severity of adverse reactions between the two methods of administration.

Additional Long-Term Experience with Kuvan

Keil et al. have conducted a retrospective study to collect data on the long-term metabolic outcomes of patients with PKU who had been treated with Kuvan or tetrahydrobiopterin (BH_4) (Schirks Laboratories, Jona, Switzerland) for at least 6 months.[8] A cohort of 147 patients, treated with either BH_4 or Kuvan alone (n=94) or either BH_4 or Kuvan in combination with a low-Phe diet (n=53), were followed for periods lasting up to 12 years. In patients receiving Kuvan for 3 years, BH_4 supplementation was used during the first year. If metabolic control was achieved, treatment regimens could be changed from treatment with Kuvan/BH_4 plus a low-Phe diet to treatment with BH_4/Kuvan alone.

In patients treated with either BH_4 or Kuvan alone, patients were, on average, 9.4 years (± 7.8) at the time when treatment was started.[8] The mean daily dose of BH_4/Kuvan at the time of data collection was 10.8 mg/kg/day (± 5.3), and patients were treated for an average duration of 4.2 years (range, 6 months – 8.8 years). The median blood Phe concentration during treatment was 276 µmol/L (range, 150 – 590 µmol/L).

Treatment regimens including either BH_4 or Kuvan in combination with a low-Phe diet were initiated at a mean age of 10.4 years (± 9.2), and patients were treated on average for 5.7 years (± 2.7).[8] At the time of last data collection, the mean dose of BH_4/Kuvan administered daily was 13.8 mg/kg (±4.8). The median blood Phe concentration during the treatment period was 308 µmol/L (range, 135-666 µmol/L).

Data on daily Phe tolerance were available on a subset of 38 patients.[8] The median tolerance prior to initiating therapy with BH_4/Kuvan was 500 mg/day (range, 200-800 mg/day) increasing to 2500 mg/day (range, 1500-3000 mg/day, $p<0.001$) upon initiation of treatment. No severe AEs were reported, and all AEs abated after lowering the BH_4/Kuvan dose.

Another retrospective study assessing the effect of Kuvan on stabilizing blood Phe levels was performed in 37 known Kuvan responders; 22 with mild to moderate PKU and 17 with classical PKU.[9] The mean Kuvan dose administered over the average follow-up period of 19 months was 20.1 mg/kg/day. An average of 39 observations (Phe levels, range, 13-96) was available on each patient.

Prior to therapy with Kuvan, the mean Phe level for all patients was 6.67 mg/dL (± 4.20), which decreased to 5.16 mg/dL (± 3.78, $p=0.0002$) after treatment had been initiated.[9] The within subject variances of Phe were 6.897 mg/dL (± 0.43) prior to Kuvan and 4.799 mg/dL (± 0.27) after. The difference in the variability of Phe levels pre- and post-Kuvan therapy was statistically significant ($p=0.0017$).

A separate study involving 14 patients with PKU examined the impact of Kuvan on metabolic control. Phe concentrations in dried blood samples were assessed beginning 1 year before the initiation of BH_4 supplementation, during the first 42 days of treatment, and after 3 months of therapy.[10] In this last phase, patients with a reduction in Phe levels of >30% and/or Phe levels

that remained within the recommended range when Phe consumption increased by 100% were considered to be BH_4-responsive and continued with treatment. Separate analyses were then performed for the BH_4 responders (n=8).

Dietary Phe tolerance in the 8 BH_4-responsive patients increased from 629 mg (± 476) at baseline to 2131 mg (± 1084, p=0.006) after the final 3-month follow-up period.[10] Phe levels remained stable over the study period despite the increase in dietary Phe (baseline, 283 µmol/L ± 145; follow-up, 304 µmol/L ± 136, p=1.0). Six of these 8 patients were able to discontinue their Phe-restricted diet.

Lastly, the clinical courses of seven patients with PKU managed with both diet and Kuvan were recently described by Gokmen Ozel et al.[11] The patients ranged in age from 3 months to 27 years of age. The first of these five patients was a 14-year old with previous reluctance to eat low protein food. Initiation of Kuvan decreased blood Phe and increased Phe tolerance, improving his overall energy intake, growth and physical activity. Similarly, in the second patient, a 7-year old girl, addition of Kuvan decreased blood Phe and increased dietary Phe tolerance, allowing introduction of vegetables, fruits, sausage, and normal bread into her diet. Another patient started Kuvan at the age of 4 years, after being diagnosed with PKU. Her blood Phe levels remained within the target range during the first 11 weeks of treatment (median level = 285 µmol/L) but slowly increased over the following 6 weeks, during which time the patient had frequent episodes of fever and dental abscesses. Kuvan was eventually stopped due to frequent illness. A fourth patient was a 27-year old female adherent to a Phe-restricted diet throughout childhood. After starting Kuvan, her mean blood Phe levels decreased; there was no change in her dietary Phe intake. Patient five was a 19-year old female who had difficulty maintaining a blood Phe level < 600 µmol/L with dietary restriction alone. After initiating therapy with Kuvan, she was able to relax her diet significantly, including the addition of normal dairy products and bread, while still keeping her Phe levels reduced by about 40% of baseline. The sixth patient initiated treatment with Kuvan at 3 months of age following a positive response to a BH_4 loading test. By the age of 9 months, the patient no longer required restriction of natural protein and maintained good metabolic control with Kuvan alone. Lastly, a 12-year old girl with type 1 diabetes experienced an increase in natural protein intake associated with Kuvan therapy.

Guidelines and Recommendations for the Long-term Use of Kuvan

In 2011, a discussion was held to assess the role of Kuvan in the long-term management of patients with PKU, and the recommendations from this meeting were reported by Cunningham et al.[12] According to these recommendations, once a patient has been identified as a responder to Kuvan and their dose of Kuvan optimized to achieve the desired Phe level, the frequency of clinic visits and follow-up assessments should be tailored to meet the needs of the individual patient. Monthly testing of blood Phe is recommended, although this frequency may depend on the age of the patient and their medical history. At each clinic visit, patients should be questioned regarding the onset of any new symptoms or potential side effects of the therapy. Overall dietary intake and dietary Phe tolerance should be assessed periodically, especially if there have been lifestyle changes or significant changes in height and/or weight. Tests should be performed routinely to evaluate metabolic status and to identify any possible nutritional deficiencies. Adjustments to both Kuvan dose and the level of dietary Phe-restriction may be required during periods of illness. Lastly, it is recommended that adherence to treatment be assessed continually,

and that patients have adequate resources and support available to them in order to optimize therapeutic outcomes. These may include, but are not limited to, peer support groups, case management services, a multidisciplinary healthcare team, referrals to specialists, and reminders for prescription refills and clinical testing.

According to the 2014 American College of Medical Genetics (ACMG) practice guidelines, "There is strong evidence to support the position that treatment and maintenance of metabolic control throughout life is essential to optimal function of individuals with PAH deficiency…Therefore it is recommended that patients be maintained in metabolic control as they move into adulthood".[13] In previous decades, management of PKU became more relaxed as patients aged with regard to dietary Phe-restriction and metabolic control. However, with more data acknowledging the negative effect of Phe on neurocognitive function, the ACMG recommend that treatment for PAH deficiency be lifelong, with blood Phe levels maintained in the range of 120-360 µmol/L, regardless of the age of the patient.

These practice guidelines recognize that an improvement in neuropsychiatric symptoms or increase in Phe tolerance without a decrease in blood Phe justifies therapy continuation.[13] They also state that for patients who are able to maintain blood Phe levels in the desired range with dietary treatment alone, sapropterin can increase dietary protein intake and Phe tolerance in responsive patients, up to two- to three-fold above baseline in some patients. For most sapropterin-responsive patients, the benefits of treatment are such that long term therapy with sapropterin should be maintained.

The primary goal of therapy is to lower blood Phe level.[13] Secondary goals include improved dietary Phe tolerance, amelioration of symptoms, and improved quality of life.

INDICATION(S)

Kuvan is indicated in conjunction with a Phe-restricted diet to reduce blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin-(BH4)-responsive Phenylketonuria (PKU).

IMPORTANT SAFETY INFORMATION

Some patients who are receiving Kuvan while following a Phe-restricted diet can experience significant drops in blood Phe levels. Blood Phe levels must therefore be carefully monitored to ensure blood Phe levels are being adequately controlled.

Adverse events (AEs) reported during Kuvan clinical trials (involving a total of 579 PKU patients) were mild and transient in nature. The most common AEs included headache, diarrhea, abdominal pain, upper respiratory tract infection, pharyngolaryngeal pain, vomiting and nausea. About one-half (54%) of the Kuvan-treated patients reported at least one AE. No Kuvan-treated patients discontinued treatment due to an AE during the clinical trials.

Patients with primary BH4 deficiency taking Kuvan and levodopa may experience over-stimulation and irritability.

If you have additional questions or if you received this information and did not specifically request this information, please contact the BioMarin Medical Information Services by phone (800) 983-4587 or (651) 523-0310, fax (866) 524-0038 or email medinfo@bmrn.com.

To report an adverse event, please contact the BioMarin Drug Safety Department by phone +1 (415) 506-6179, fax +1 (415) 532-3144, or email drugsafety@bmrn.com.

Sincerely,

Jessica Cohen-Pfeffer, M.D.
Associate Medical Director
Medical Affairs
BioMarin Pharmaceutical Inc.
www.bmrn.com
Case 1-36727847

ENCLOSURE(S)

Kuvan [product monograph]. Toronto, Ontario: BioMarin Pharmaceutical (Canada) Inc.; Rev. April, 2010.

REFERENCE(S)

1. Data on File, BioMarin Pharmaceutical Inc.

2. Burton BK, Grange DK, Milanowski A, et al. The response of patients with phenylketonuria and elevated serum phenylalanine to treatment with oral sapropterin dihydrochloride (6R-tetrahydrobiopterin: a phase II, multicentre, open-label screening study. *JIMD*. 2007;30(5):700-707.

3. Levy HL, Milanowski A, Chakrapani A, et al. Efficacy of sapropterin dihydrochloride (tetrahydrobiopterin, 6R-BH4) for reduction of phenylalanine concentration in patients with phenylketonuria: a phase III randomized placebo-controlled study. *Lancet*. 2007;370:504-510.

4. Lee P, Treacy EP, Crombez E, Wasserstein M, et al. 2008. Safety and efficacy of 22 weeks of treatment with sapropterin dihydrochloride in patients with phenylketonuria. *Am J Med Genet Part A* 146A:2851–2859.

5. Trefz FK, Burton BK, Long N, et al. Efficacy of sapropterin dihydrochloride in increasing phenylalanine tolerance in children with phenylketonuria: A phase III, randomized, double-blind, placebo-controlled study. *J Pediatr*. 2009;154:700-707.

6. Longo N, Siriwardena K, Feigenbaum A, et al. Long-term development progression in infants and young children taking sapropterin for phenylketonuria: A two-year analysis of safety and efficacy. *Genet Med.* Submitted.

7. Burton BK, Nowacka M, Hennermann JB, et al. Safety of extended treatment with sapropterin dihydrochloride in patients with phenylketonuria: Results of a phase 3b study. *Mol Genet Metab*. 2011;103:315-322.

8. Keil S, Anjema K, van Spronsen FJ, et al. Long-term follow-up and outcome of phenylketonuria patients on sapropterin: a retrospective study. *Pediatrics*. 2013;131(6):e1881-1888.

9. Burton BK, Bausell H, Katz R, LaDuca H, Sullivan C. Sapropterin therapy increases stability of blood phenylalanine levels in patients with BH_4-responsive phenylketonuria. *Mol Genet Metab*. 2010;101:110-114.

10. Ziesch B, Weigel J, Thiele A, et al. Tetrahydrobiopterin (BH_4) in PKU: effect on dietary treatment, metabolic control and quality of life. *J Inherit Metab Dis*. 2012;35:983-992.

11. Gokmen Ozel H, Lammardo AM, Motzfeldt K, et al. Use of sapropterin in the management of phenylketonuria: Seven case reports. *Mol Genet Metab*. 2013;108:109-111.

12. Cunningham A, Bausell H, Brown M, et al. Recommendations for the use of sapropterin in phenylketonuria. *Mol Genet Metab*. 2012;106:269-276.

13. Vockley J, Andersson HC, Antshel KM, et al. Phenylalanine hydroxylase deficiency: diagnosis and management guideline. *Genet Med*. 2014;16:188-200.

Version 1.0 (CA)
Updated: May 12, 2014