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CA16-00038 (SE)

Dear Nicole Pallone,

Thank you for contacting BioMarin regarding Kuvan® (sapropterin dihydrochloride). This letter is provided in response to your inquiry. You asked for information regarding the use of Kuvan in patients under the age of 8 years, specifically the PKU-015 and Safety Pediatric EfficAcy PhaRmacokinetic with Kuvan **(**SPARK) studies. Please find below the information that we have in patients <4 years of age, which include these 2 studies.

USE OF KUVAN IN PATIENTS UNDER 4 YEARS OF AGE

While there is no age restriction in the approved labeling, data concerning the use of Kuvan in patients <4 years of age are limited. Please find below data available regarding the use of Kuvan in this patient population.

Summary

- In the SPARK Study, mean phenylalanine (Phe) tolerance increased significantly after 26 weeks of Kuvan treatment.[1,2]

- In the PKU-015 Study, after 24 months of Kuvan treatment in combination with a Phe-restricted diet, 87% of patients had ≥30% mean Phe reduction from baseline. No statistically significant changes in mean Full Scale Intelligence Quotient (FSIQ) and standard z-scores for height, weight, and head circumference were detected.[3]

- In the Phenylketonuria Demographics Outcomes and Safety (PKUDOS) registry, median blood Phe level decreased by 22%, 26% and 42% after 1, 2, and 3 years from baseline, respectively.[4,5] Respective increases in dietary Phe values were 97%, 141%, and 26%.

- The American College of Medical Genetics and Genomics (ACMG) recommends that treatment of patients with phenylketonuria (PKU) should be initiated as soon as possible after diagnosis, preferably within the first week of life.[6]

Labeling Information

Pediatric patients with PKU, ages 4 to 16 years, have been treated with Kuvan in clinical studies.[7] The safety and efficacy of Kuvan in pediatric patients less than 4 years of age have not been established in clinical trials. Frequent blood monitoring is recommended in the pediatric population to ensure adequate blood Phe level control.

Clinical Trial Experience

SPARK Trial

This is an ongoing, open-label, randomized, Phase 3b study being conducted in Europe to assess the efficacy, safety and population pharmacokinetics of Kuvan in children <4 years of age with a diagnosis of PKU and a positive response test to Kuvan.[1,2] Patients are being treated with either Kuvan 10 mg/kg/day in addition to a Phe-restricted diet (n=27, 21.1±12.3 months) or diet alone (n=29, 21.2±12.0 months). At baseline, mean Phe tolerance was 37.1±17.3 mg/kg/day in patients treated with Kuvan and diet and 35.8±20.9 mg/kg/day in patients treated with diet alone. At 26 weeks, these values were 80.6±4.2 and 50.1±4.3 mg/kg/day, respectively ($p<0.001$). The safety profile was comparable in both groups, with rhinitis and vomiting being the most frequently reported adverse events (AEs) related to Kuvan. The long-term efficacy and safety of Kuvan will be assessed in the study's optional 3-year extension period.

PKU-015 Study

This on-going, multicenter, open-label study is designed to evaluate the safety and efficacy of Kuvan in patients aged 0 to 6 years of age at study entry, specifically by exploring the long-term effect of Kuvan on preserving neurocognitive function.[3] Secondary outcome measures evaluate the efficacy of Kuvan treatment in controlling blood Phe concentration, its effect on growth parameters, and its long-term safety profile.

Children enroll in the study initially receive Kuvan 20 mg/kg/day and follow a Phe-restricted diet to maintain blood Phe levels within the site-specific recommended ranges, with a goal of keeping blood Phe concentration between 120-240 µmol/L.[3] FSIQ is the primary efficacy endpoint, with cognitive outcomes assessed using the following age-specific tools: Bayley Scales of Infant and Toddler Development, 3rd ed. (0 to <30 months), Wechsler Preschool and Primary Scale of Intelligence, 3rd ed. (WPPSI-III; age ≥30 months to <7 years) and Wechsler Intelligence Scale for Children, 4th ed. (WISC-IV; age ≥7 years). The study will be considered complete when approximately 45 patients have completed 7 years of treatment.

An interim analysis has been performed on data collected in a subset of patients who responded to Kuvan therapy and had completed at least 2 years in the study as of June 2012, as well as 3 patients who terminated the study before the 2-year timepoint.[3] Of the 95 children enrolled in the study, 71 were identified as responders to Kuvan (≥30% average reduction in blood Phe) during the first 4 weeks of the study. Of these children, 65 continued on to the 6-month safety and efficacy assessment, and 63 continued past 6 months and were enrolled in the long-term evaluation of neurocognitive function. A total of 55 patients had data available for the 2-year interim analysis.

The mean age at enrollment was 3.1±2.2 years, with a breakdown in age as follows: <1 year, n=10; 1-2 years, n=19; 3-4 years, n=13; 5-6 years, n=13.[3] The mean baseline blood Phe level for all age groups was 331.2±138.3 µmol/L. Of 55 children with 24-month follow-up data, 48 (87%) were 'per-protocol' responders to Kuvan (≥30% mean Phe reduction from baseline), whereas the remaining patients were considered to be 'clinical' responders (<30% mean blood Phe reduction, but blood Phe maintained between 120-360 µmol/L, despite increased dietary Phe intake). The average daily dose of Kuvan was 20.3 mg/kg, which varied little across age groups.

At baseline, mean blood Phe levels were ≤240 µmol/L and ≤360 µmol/L in 33% (n=18/55) and 65% (n=36/55) of children, respectively.[3] After 24 months of treatment with Kuvan in combination with a Phe-restricted diet, this value increased to 64% (n=32/50) and 84% (n=42/50), respectively. Prescribed dietary Phe increased from baseline to 2 years in all age groups. After 4 weeks of therapy, due to an increase in prescribed dietary Phe which was allowed at Week 5 visit to maintain blood Phe level in the targeted range, there was an increase in blood Phe levels.

An analysis of data from the 25 children for whom baseline and 24-month WPPS-III and WISC-IV scores were available revealed mean FSIQ scores at baseline (103±12); no statistically significant change in mean FSIQ was detected after 24 months of treatment with Kuvan (104±10; p=0.50).[3] Mean scores on the Bayley-III Cognitive Composite Index were also maintained within the normal range of 100±15, with no significant changes over time; there was no infant or toddler receiving a score of less than 85. Standard z-scores for height, weight and head circumference were also maintained throughout the 2 years of follow-up, with no statistically significant changes from baseline.

Safety outcomes associated with Kuvan therapy were consistent with those reported in patients older than 4 years of age.[3,8,9] The most common AEs (occurring in >5% of subjects) classified as possibly or probably related to Kuvan were abdominal pain, diarrhea, vomiting, infections of the ear and upper respiratory tract, nasal congestion and headache.[3] Six serious AEs (SAE), which included constipation, croup, pneumonia, injury, anesthesia complication and seizure, were reported in 5 children; none of the SAEs were determined to be related to treatment with Kuvan.

PKUDOS Registry

This is a Phase 4, observational study designed to provide 15 years of follow-up data in patients with PKU who have been treated with Kuvan, are currently receiving Kuvan or intend to receive Kuvan within 90 days of entering the registry.[4,5] The age distribution of the patients, based on first Kuvan dose, ranged from 0-63 years; 97 (8%) patients were <4 years of age.

The data presented here focus on the 58 patients who were initially treated with Kuvan at less than 4 years of age.[4,5] Forty-eight of these patients were treated continuously with Kuvan and made up the 'uninterrupted use' population. An additional 10 patients discontinued treatment within 3 months and made up the 'short-term' use population. The mean age of the uninterrupted use patients (1.8±1.2 years) was similar to that of the short-term use population (1.9±1.2 years).

The pre-Kuvan baseline mean of median blood Phe level was 259 µmol/L in the uninterrupted use group, a value which decreased by 22%, 26% and 42% after 1, 2, and 3 years from baseline, respectively.[4,5] In the short-term use population, values decreased by 13%, 50%, and 39%, respectively, from a baseline mean of median of 369 µmol/L. Dietary Phe increased by 97%, 141%, and 26% after 1, 2, and 3 years from baseline (median, 292 mg/day), respectively, in the uninterrupted group, and by 110%, 99%, and 262% from baseline (median, 183 mg/day), respectively, in the short-term use patients.

At the time of interim analysis, AEs (n=4) were reported in 6% of patients <4 years of age (n=69), with no SAEs reported in this age group.[4] All of the AEs were mild in severity, with 3

occurring in patients actively treated with Kuvan and 1 occurring in a patient off of therapy. Both the gastrointestinal (n=2; diarrhea, unspecified gastrointestinal disorder) and respiratory systems (n=2; dysphonia and rhinorrhea) were affected. No neurological events were reported in patients <4 years of age.

Other Studies

The use of Kuvan in this patient population has been described in other smaller studies (Table 1).

Table 1. Summary of Studies Regarding the Use of Kuvan in PKU Patients <4 Years of Age

Study	Patient demographics	Dose/Duration	Findings
Keil, et al.[10] (N=147)	• 100 were minors, mean age 9.5±4.3 years (range, 1-17 years) • 94 patients received treatment with BH_4/Kuvan • 53 patients received treatment with BH_4/Kuvan and diet	• Mean current daily dose for BH_4/Kuvan only: 10.8±5.3 mg/kg/day • Mean current daily dose for all patients: 13.8±4.8 mg/kg/day • Treatment duration, 5.7±2.7 years (range, 2.0-12.0 years)	• Median blood Phe levels within range for all patients • Median Phe tolerance increased 3.9 folds with BH_4/Kuvan therapy compared with dietary treatment • 49.6% of patients treated with BH_4/Kuvan reported improvements in quality of life compared to patients treated with diet alone • 63.3% improvement in compliance with BH_4/Kuvan treatment as compared to diet alone • 85 different patient genotypes were identified; all but 2 were associated with a decrease in Phe hydroxylase activity • No serious AEs reported
Burton, et al.[11] (N=37)	• BH_4-responsive patients • Mean age, 12.6 years (range, 1.5-32 years)	• Mean dose, 20.1 mg/kg/day • Mean duration, 19 months (range, 12-31 months)	• Mean±SD Phe levels before and after Kuvan therapy were 6.67±4.2 and 5.16±3.78 mg/dL, respectively, (p=0.0002) • Within subject variances of Phe were 6.897±0.43 prior to therapy and 4.799±0.27 post-Kuvan therapy (p=0.0017)
Unal, et al.[12] (N=34)	• Sapropterin-responsive patients <4 years of age • Mean age, 2.3 years	• Median duration, 17.8 months	• Liberalization of diet achieved in 27 patients (79.4%) • Median Phe tolerance increased by 2.47 folds (range, 1.21-5.63 folds) • No AEs reported
Couce, et al.[13] (N=16)	• BH_4-responsive patients • 7 patients started treatment before 4 years of age	• Mean dose, 9.75±0.9 mg/kg/day (range, 8-12.5 mg/kg/day) • Mean follow-up of 62 months	• Patients who began treatment within 1 month of birth (n=5): ▪ Significant increases in Phe tolerance up to 550 mg/day ▪ All patients maintained Phe levels within the optimal range (mean, 171±98 µmol/L) • Patients who started treatment after the neonatal period (n=11): ▪ Minimum 24% increase in dietary Phe tolerance ▪ All patients maintained Phe levels within appropriate range for age ▪ 1 AE noted, an incident of vomiting
Trefz, et al.[14] (N=16)	• BH_4-responsive patients: • 10 patients were <4 years	• Mean dose, 16 mg/kg/day (range, 5-36 mg/kg/day • Mean duration, 56 months (range, 24-110 months)	• Long-term Phe control achieved in 14 patients with mean decrease in blood Phe from baseline of 54.6% • Of 7 patients who required continued diet restriction, Phe intake increased from 200-300 mg/day to 800-1000 mg/day • No side effects related to treatment were observed

Study	Patient demographics	Dose/Duration	Findings
Leuret, et al.[15] (N=15)	• BH_4-responsive patients <4 years of age • Mild PKU, baseline Phe between 600-1200 µmol • 7 patients treated as neonates, 8 patients initiated therapy at a mean age of 13±12 months (range, 5-35 months)	• 20 mg/kg/day (range, 8-24 mg/kg/day) • Duration of 23 months (range, 7-80 months)	• Improvement in dietary Phe tolerance with a 4-fold increase in Phe intake (456±181 vs 1683±627 mg/day, p<0.0001) • Increase in natural protein intake allowed discontinuation of Phe-free amino acid mixture in 7 patients • Improvement in metabolic control (352±85 vs 254±64 µM, p<0.05) • Increase within therapeutic range Phe values (64±16% vs. 35±25%, p<0.05) • Reduction in phenylalaninemia variance (130±21 vs. 93±27 µM, p<0.05) • No AEs reported
Stockler-Ipsiroglu, et al.[16] (N=11)	• Aged 1 month to 16 years	• Median duration, 26 months (range, 13-44 months) • Doses, 15-20 mg/kg/day	• After 1 month, reductions in Phe as compared to baseline ranged from 30% to 69% (median, 49%) • After 6 months, 7 patients continued to maintain a mean blood Phe reduction >30% as compared to 6 month pretreatment values (range, 33% to 68%; median, 47%) • Six of these 7 patients also had an increase in mg/kg/day Phe tolerance • All patients assessed had an increase in total mg/day dietary Phe tolerance (range, 8%-212%; median, 78%)

AEs, adverse events; BH_4, tetrahydrobiopterin; N/n, number of patients; Phe, phenylalanine; PKU, phenylketonuria; SD, standard deviation

Guidelines on the Use of Kuvan in Patients <4 Years of Age

According to the practice guidelines published by the ACMG, treatment of patients with PKU should be initiated as soon as possible after diagnosis, preferably within the first week of life.[6] According to the guideline's authors, the goal of early treatment is the same for all patients with PKU, to have blood Phe levels maintained within the range of 120-360 µmol/l; further normalization of levels within the range of 60-120 µmol/L should not be considered "too low." All patients, especially newly diagnosed infants, should have their Phe and tyrosine (Tyr) levels monitored frequently until the levels have stabilized, after which time, blood Phe should be monitored at least weekly until patients have reached 1 year of age; increased surveillance is also recommended during periods of rapid growth and following changes in diet, including the introduction of solid foods to infants. After the first year, biweekly to monthly Phe testing is often sufficient.

Experience in the use of sapropterin in children under the age of 4 has been gained in the treatment of phenylalanine hydroxylase (PAH) deficiency.[6] Sapropterin responsiveness is typically assessed prior to initiating therapy in these patients by administering a dose of tetrabiopterin (BH_4) and monitoring the change in Phe levels over periods lasting from 24 hours to 3 or 4 weeks. Significant decreases in Phe, increases in dietary Phe tolerance or improvement in clinical symptoms are all indicators of responsiveness and support ongoing treatment with sapropterin.

The risk of neurocognitive or psychological manifestations of PAH deficiency is associated with the age at which treatment is initiated, long-term Phe control and adherence to treatment regimens.[6] Early and ongoing treatment and maintenance of metabolic control is therefore critical to the optimal health and social functioning of these patients. Patients who are well controlled at an early age are protected against intellectual disability. However, relaxation of Phe control in childhood has been associated with a variety of detrimental neurocognitive and psychiatric outcomes later in life.

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INDICATION(S) AND IMPORTANT SAFETY INFORMATION

Please refer to the attached product labeling.

PHENYLKETONURIA DEMOGRAPHIC, OUTCOMES, AND SAFETY REGISTRY (PKUDOS)

As part of our post-marketing commitment to regulatory authorities, BioMarin has established the PKUDOS registry, a Phase 4, observational, voluntary, multicenter study designed to provide 15 years of follow-up data in patients with PKU who have been treated with Kuvan, are currently receiving Kuvan, or intend to receive Kuvan within 90 days of entering the registry. It includes a sub registry, called PKU MOMS (Maternal PKU Observational Program) that collects information on pregnant women who are on or have been exposed in the past to Kuvan and their offspring. For more information about the registry, please email PKUDOS@bmrn.com.

BioMarin Pharmaceutical Inc. recommends the use of its products in a manner consistent 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 product label(s) for Important Safety Information, specifics relating to dosing, and other important considerations.

As a pharmaceutical company, BioMarin is unable to provide medical advice or clinical information directly to patients or their families. For questions regarding treatment decisions, please refer interested parties to the appropriate healthcare provider.

If you have additional questions, please contact BioMarin Medical Information by phone (800) 983-4587 or (651) 523-0310, fax (866) 524-0038, or email medinfo@bmrn.com.

Sincerely,

Medical Information,
BioMarin Pharmaceutical Inc.

ENCLOSURE(S)
KUV Labels Canada EN PM-CLEAN-04-DEC-2014