PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr Kuvan®

(sapropterin dihydrochloride)

100 mg Tablets

Alimentary Tract and Metabolism Products

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PrKuvan®
(sapropterin dihydrochloride) Tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet 100 mg	*For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.*

INDICATIONS AND CLINICAL USE

Kuvan® (sapropterin dihydrochloride) 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).

Geriatrics (65 years and older): Clinical studies of Kuvan in patients with PKU did not include patients aged 65 years and older. It is not known whether these patients respond differently to Kuvan than younger patients.

Pediatrics (less than 16 years of age): Pediatric patients with PKU, ages 1 month to 16 years, have been treated with Kuvan in clinical studies [see CLINICAL TRIALS].

CONTRAINDICATIONS

Patients who are hypersensitive to this drug or to any ingredient in the formulation, or to any component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.

WARNINGS AND PRECAUTIONS

General

Monitor Blood Phe Levels During Treatment

Treatment with Kuvan should be directed by physicians knowledgeable in the management of PKU. Prolonged elevations in blood Phe levels in patients with PKU can result in severe neurologic damage, including severe mental retardation, microcephaly, delayed speech, seizures, and behavioural abnormalities. This may occur even if patients are taking Kuvan but not adequately controlling their blood Phe levels within the recommended target range. Conversely, prolonged levels of blood Phe that are too low have been associated with catabolism and protein

breakdown. Active management of dietary phenylalanine and overall protein intake while taking Kuvan is required to ensure adequate control of blood phenylalanine and tyrosine levels and nutritional balance.

Monitor blood Phe levels during treatment to ensure adequate blood Phe level control. Frequent blood monitoring is recommended in the pediatric population.

Consultation with a physician is recommended during illness as blood phenylalanine levels may increase.

There are limited data regarding the long-term use of Kuvan (see ADVERSE REACTIONS and Part II: Clinical Trials). Neurocognitive outcomes with Kuvan treatment have not been established in long term clinical studies.

Treat All Patients With a Phe-restricted Diet

All patients with PKU who are being treated with Kuvan should also be treated with a Phe-restricted diet. The initiation of Kuvan therapy does not eliminate the need for appropriate monitoring by trained professionals to assure that blood Phe control is maintained in the context of ongoing dietary management.

Hypophenylalaninemia

In clinical trials, some patients have experienced low blood Phe levels (see WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics). Children younger than 7 years and infants less than one year of age who were treated with Kuvan doses of 10 mg/kg/day to 20 mg/kg/day had higher rates of low levels of blood Phe compared with older children.

Prolonged exposure to low blood phenylalanine and tyrosine levels during infancy has been associated with impaired neurodevelopmental outcome.

Identify Non-Responders to Kuvan Treatment

Not all patients with PKU respond to treatment with Kuvan. In two clinical trials at a dose of 20 mg/kg per day, 56% to 66% of pediatric PKU patients responded to treatment with Kuvan. In one clinical trial at a dose of 10 mg/kg per day, 20% of adult and pediatric PKU patients responded to treatment with Kuvan [see CLINICAL TRIALS]. Response to treatment cannot be pre-determined by laboratory testing (e.g. molecular testing), and should only be determined by a therapeutic trial of Kuvan [see DOSAGE AND ADMINISTRATION].

Cardiovascular

Use with Drugs Known to Affect Nitric Oxide-Mediated Vasorelaxation

BH4 is a cofactor for nitric oxide synthetase. Both sapropterin dihydrochloride and PDE-5 inhibitors may induce vasorelaxation, and the additive effect of sapropterin and PDE-5 inhibitor co-administration could lead to a reduction in blood pressure; however, the combined use of these medications has not been evaluated in humans.

Caution and monitoring of blood pressure is advised when administering Kuvan with all medicinal products that cause vasodilation, including those administered topically, by affecting

nitric oxide (NO) metabolism or action including classical NO donors (e.g. glyceryl trinitrate (GTN), isosorbide dinitrate (ISDN), sodium nitroprusside (SNP), molsidomin), phosphodiesterase type 5 (PDE-5) inhibitors and minoxidil.

Endocrine and Metabolism

Use with Medications Known to Inhibit Folate Metabolism

Drugs known to affect folate metabolism (e.g. methotrexate) and their derivatives should be used with caution while taking Kuvan because these drugs can decrease BH4 levels by inhibiting the enzyme dihydropteridine reductase (DHPR). Although concomitant administration of inhibitors of dihydrofolate reductase (e.g. methotrexate, trimethoprim) has not been studied, such medicinal products may interfere with BH4 metabolism. More frequent monitoring of blood Phe levels may be required when administering Kuvan with drugs known to inhibit folate metabolism.

Gastrointestinal

Gastritis

During clinical studies, gastritis was reported as a serious adverse reaction. Monitor patients for signs and symptoms of gastritis (see ADVERSE REACTIONS).

Hepatic

Use with Caution in Patients with Hepatic Impairment

Patients with liver impairment have not been evaluated in clinical trials with Kuvan. Patients who have liver impairment should be carefully monitored when receiving Kuvan because hepatic damage has been associated with impaired Phe metabolism.

Immune

Hypersensitivity Reactions Including Anaphylaxis

Kuvan is contraindicated in patients with a history of anaphylaxis to Kuvan (see CONTRAINDICATIONS). Hypersensitivity reactions, including anaphylaxis and rash, have occurred [see ADVERSE REACTIONS]. Signs of anaphylaxis include wheezing, dyspnea, coughing, hypotension, flushing, nausea, and rash. Discontinue treatment with Kuvan in patients who experience anaphylaxis and initiate appropriate medical treatment. Continue dietary Phe restrictions in patients who experience anaphylaxis.

Neurologic

Use With Caution When Co-administering Kuvan and Levodopa

Caution should be used with the administration of Kuvan to patients who are receiving levodopa. In a 10 year post-marketing safety surveillance program for a non-PKU indication using another formulation of the same active ingredient (sapropterin), 3 patients with underlying neurologic disorders experienced seizures, exacerbation of seizures, over-stimulation, or irritability during co-administration of levodopa and sapropterin. Monitor for change in neurologic status.

Hyperactivity

In the post-marketing safety surveillance program for PKU, some patients experienced hyperactivity with administration of Kuvan. Monitor patients for hyperactivity [see OVERDOSAGE].

Seizures
Caution is advised when Kuvan is used in patients with predisposition to seizures. Events of seizure and exacerbation of seizure have been reported in such patients.

Renal
Patients with renal impairment have not been evaluated in clinical trials. Patients who have renal impairment should be carefully monitored when receiving Kuvan.

Special Populations

Pregnant Women:
In rabbits, there was a non-statistically significant increase in the incidence of holoprosencephaly at the 600 mg/kg/day dose. (See Part II: TOXICOLOGY).

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the expected benefits outweigh the risks. Elevated Phe levels in pregnant women are teratogenic and can cause significant congenital brain and cardiac damage in babies of PKU-affected mothers, known as Maternal PKU Syndrome. Available data from the Maternal Phenylketonuria Collaborative Study on 468 pregnancies and 331 live births in PKU-affected women demonstrated that uncontrolled Phe levels (above 600 μmol/L) are associated with a very high incidence of neurological, cardiac, facial dysmorphism, and growth abnormalities in babies of PKU-affected mothers. Good dietary control of Phe levels during pregnancy is essential to reduce the incidence of Phe-induced teratogenic effects.

Maternal blood phenylalanine levels must therefore be strictly controlled before and during pregnancy. If maternal phenylalanine levels are not strictly controlled before and during pregnancy, this could be harmful to the mother and the foetus. Physician-supervised restriction of dietary phenylalanine intake prior to and throughout pregnancy is the first choice of treatment in this patient group.

The use of Kuvan should be considered only if strict dietary management does not adequately reduce blood phenylalanine levels. Caution must be exercised when prescribing to pregnant women.

Labor and Delivery: The effects of Kuvan on labor and delivery in pregnant women have not been studied. Kuvan use during labor and delivery is not recommended.

Nursing Women: Sapropterin dihydrochloride is excreted in the milk of intravenously, but not orally, treated lactating rats. It is not known whether sapropterin is excreted in human breast milk. 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, Kuvan should not be administered during lactation.

Pediatrics (less than 16 years of age):
Pediatric patients with PKU, ages 1 month to 16 years, have been treated with Kuvan in clinical studies [see CLINICAL TRIALS]. The efficacy and safety of Kuvan have not been established in children less than 1 month of age.

Children younger than 7 years and infants less than one year of age treated with Kuvan are at increased risk for low levels of blood Phe compared with older children. Frequent blood monitoring is recommended in the pediatric population to ensure adequate blood Phe level control. See Hypophenylalaninemia.

Geriatrics (65 years and older): Clinical studies of Kuvan in patients with PKU did not include patients aged 65 years and older. It is not known whether these patients respond differently to Kuvan than younger patients. Caution must be exercised when prescribing to geriatric patients.

Monitoring and Laboratory Tests
Patients being treated with Kuvan should have frequent blood Phe level measurements and dietary guidance from a dietitian to ensure maintenance of blood Phe levels in the desirable range [1].

ADVERSE REACTIONS

Adverse Drug Reaction Overview
The safety of Kuvan was evaluated in 7 clinical studies in patients with PKU (aged 1 month to 50 years).

In clinical trials (PKU-001, PKU-003, PKU-004, PKU-006, PKU-008), 579 PKU patients received Kuvan in doses ranging from 5 to 20 mg/kg/day for lengths of treatment ranging from 1 to 30 weeks. Patients were aged 4 to 49 years old. The patient population was nearly evenly distributed in gender, and approximately 95% of patients were Caucasian. No deaths were reported. 310 (54%) of the Kuvan-treated patients reported at least one adverse event (AE). 5 patients (1%) reported the following serious adverse events (SAEs) (regardless of relationship to treatment): appendicitis, urinary tract infection, gastroesophageal reflux disease, spinal cord injury, tibia fracture, streptococcal infection, and testicular carcinoma. The most commonly reported AEs (in ≥ 4% of the Kuvan-treated patients) were: headache (13%), diarrhoea (6%), abdominal pain (6%), upper respiratory tract infection (5%), pharyngolaryngeal pain (5%), vomiting (4%), and nausea (4%). No Kuvan-treated patients discontinued treatment due to an AE during the clinical trials.

In an open-label study (SPARK, n=56) in children aged 2 months to 4 years treated with Kuvan 10 mg/kg/day to 20 mg/kg/day for up to 6 months, the following SAEs were reported in Kuvan-treated patients: gastroenteritis, rash, overdose, and stomatitis. Low blood Phe levels were also reported in Kuvan-treated pediatric subjects in the SPARK study and in an additional open-label study (PKU-015) in children aged 1 month to 6 years treated with Kuvan 20 mg/kg/day for up to 6 months. See **Clinical Trial Adverse Drug Reactions**.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In two double-blind, placebo-controlled trials (PKU-003 and PKU-006), 74 patients were treated with Kuvan while 59 patients were treated with placebo. The data described below reflect exposure of 74 PKU patients to Kuvan at doses of 10 to 20 mg/kg/day for 6 to 10 weeks. The overall incidence of adverse events in patients receiving Kuvan (64%) was similar to that reported with patients receiving placebo (71%).

Table 1 enumerates treatment-emergent adverse events that occurred in more than 1 patient (≥2%) treated with Kuvan in the double-blind, placebo-controlled clinical studies described above.

Table 1: Summary of Adverse Events by Preferred Term Occurring in ≥ 2% of Patients in Controlled Clinical Studies With Kuvan

MedDRA Preferred Term	Placebo (n=59)	Kuvan (n=74)
No. of Patients Reporting at Least One AE	42 (71.2%)	47 (63.5%)
Headache	8 (13.6%)	11 (14.9%)
Upper respiratory tract infection	14 (23.7%)	9 (12.2%)
Rhinorrhoea	0	8 (10.8%)
Pharyngolaryngeal pain	1 (1.7%)	7 (9.5%)
Diarrhoea	3 (5.1%)	6 (8.1%)
Vomiting	4 (6.8%)	6 (8.1%)
Cough	3 (5.1%)	5 (6.8%)
Pyrexia	4 (6.8%)	5 (6.8%)
Abdominal pain	5 (8.5%)	4 (5.4%)
Contusion	1 (1.7%)	4 (5.4%)
Rash	4 (6.8%)	4 (5.4%)
Nasal congestion	0	3 (4.1%)
Back pain	3 (5.1%)	2 (2.7%)
Decreased appetite	0	2 (2.7%)
Erythema	0	2 (2.7%)
Excoriation	0	2 (2.7%)
Fatigue	3 (5.1%)	2 (2.7%)
Infection	0	2 (2.7%)
Lymphadenopathy	0	2 (2.7%)
Otitis externa	0	2 (2.7%)
Pharyngitis	1 (1.7%)	2 (2.7%)
Streptococcal infection	3 (5.1%)	2 (2.7%)
Toothache	0	2 (2.7%)
Urinary tract infection	0	2 (2.7%)

In open-label, uncontrolled clinical trials (PKU-001 and PKU-004) in which all patients received Kuvan in doses of 5 to 20 mg/kg/day, AEs were similar in type and frequency to those reported in the double-blind, placebo-controlled clinical trials.

In an additional open-label extension study of Kuvan (PKU-008), 111 PKU patients were treated within a range of 5 mg/kg/day to 20 mg/kg/day to control blood Phe concentrations for an additional 18 months beyond their exposure in previous clinical studies. No deaths were reported. Four patients reported SAEs (3 unrelated and 1 possibly related case of gastroesophageal reflux disease). Two patients withdrew from the study due to an AE (difficulty concentrating and intermittent diarrhoea). Clinical laboratory results, vital sign measurements, and physical examinations did not reveal any clinically significant AE signals resulting from Kuvan treatment.

Two additional studies in children aged 1 month to 6 years were conducted. SPARK (n=56) was an open-label, controlled study in which 27 pediatric patients (2 months to <4 years of age) with PKU received Kuvan 10 mg/kg/day or 20 mg/kg/day in addition to a Phe-restricted diet for 26 weeks. PKU-015 (n=65) was an open-label uncontrolled study in which 65 pediatric patients (1 month to <6 years of age) received Kuvan 20 mg/kg per day in addition to a Phe-restricted diet for 6 months.

In the SPARK study, hypophenylalaninemia (also termed "amino acid level decreased") was experienced by 37% of subjects in the Kuvan plus Phe-restricted diet group vs. 33.0% in the Phe-restricted diet alone group. In PKU-015, 87.7% of subjects treated with Kuvan had a blood Phe levels below 120 µmol/L at some point during the study, with the highest rates in the newborn to less than 1 year of age subgroup in the first 4 weeks of treatment.

In the SPARK study, subjects who were less than 12 months old and treated with Kuvan had a greater mean decrease in platelet levels from baseline to Week 26 compared with subjects treated with Phe-restricted diet alone. No adverse events related to a decrease in platelet counts were observed in the study. The clinical significance of these findings is not known.

Less Common Clinical Trial Adverse Events (<2%)
Blood and Lymphatic System: lymphadenopathy, neutropenia
Cardiac Disorders: cardiac murmur, heart rate increased
Congenital, Familial and Genetic Disorders: ichthyosis
Eye Disorders: eye pain, lacrimation increased
Gastrointestinal Disorders: abdominal distension, abdominal pain lower, abdominal pain upper, abdominal tenderness, abnormal faeces, constipation, dry mouth, dyspepsia, flatulence, frequent bowel movements, gingival bleeding, gingival pain, haematochezia, haemorrhoids, retching, stomach discomfort, tongue spasm, gastroesophageal reflux disease (GERD), epigastric ulcer
General Disorders and Administration Site Conditions: asthenia, chest discomfort, chills, energy increased, feeling hot, influenza like illness, irritability, malaise, oedema peripheral, pyrexia, suprapubic pain, thirst
Infections and Infestations: ear infection, eye infection, herpes zoster, hordeolum, influenza,

lower respiratory tract infection, nasopharyngitis, pharyngitis, sinusitis, streptococcal infection, tooth abscess, upper respiratory tract infection, urinary tract infection
Injury, Poisoning and Procedural Complications: contusion, excoriation
Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, blood amino acid level increased, blood bilirubin increased, blood cholesterol increased, blood lactate dehydrogenase increased, blood uric acid increased, eosinophil count increased, gamma-glutamyltransferase increased, glucose urine present, neutrophil count decreased, platelet count decreased, protein urine present, urine colour abnormal, white blood cell count decreased
Metabolism and Nutrition Disorders: anorexia, decreased appetite, polydipsia
Musculoskeletal and Connective Tissue Disorders: arthralgia, back pain, muscle fatigue, myalgia, neck pain, pain in jaw
Nervous System Disorders: cluster headache, disturbance in attention, dizziness, dysgeusia, dysgraphia, hyperreflexia, hypersomnia, lethargy, migraine, psychomotor hyperactivity, sinus headache, somnolence, syncope, tremor, convulsions
Psychiatric Disorders: agitation, confusional state, distractibility, emotional disorder, insomnia, libido increased, mood altered, panic attack, paranoia, sleep disorder
Renal and Urinary Disorders: micturition urgency, pollakiuria, polyuria, nephrolithiasis
Reproductive System and Breast Disorders: menstrual disorder, vaginal haemorrhage
Respiratory, Thoracic and Mediastinal Disorders: asthma, cough, epistaxis, nasal congestion, respiratory tract congestion, rhinorrhoea, sneezing, throat irritation
Skin and Subcutaneous Tissue Disorders: dermal cyst, dermatitis allergic, dry skin, erythema, erythema multiforme, rash, rash erythematous, rash maculo-papular, rash puritic, skin odour abnormal
Vascular Disorders: hot flush, peripheral coldness

Adverse events reported were similar in type and frequency to those observed in other clinical trials, with exception of addition of the following adverse events considered to be related to Kuvan by the investigator and not listed elsewhere in the Clinical Trial Adverse Drug Reactions section:

Eye Disorders: vision blurred
Gastrointestinal Disorders: Abdominal discomfort, mouth ulceration
Infections and Infestations: gastroenteritis, rhinitis
Investigations: blood alkaline phosphatase increased, blood calcium decreased, carbon dioxide decreased, amino acid level decreased
Metabolism and Nutrition Disorders: hyponatremia
Psychiatric Disorders: anger, vomiting psychogenic
Renal and Urinary Disorders: enuresis
Respiratory, Thoracic and Mediastinal Disorders: dysphonia
Skin and Subcutaneous Tissue Disorders: hair color changes

Abnormal Hematologic and Clinical Chemistry Findings

Table 2: Clinically Significant Abnormal Changes in Hematological Test Findings Reported in Kuvan-Treated Patients

	Controlled Studies		All Kuvan-Treated (n=579)
Parameter Notable Criteria (Reference Ranges)	Placebo (n=59)	Kuvan (n=74)	
No. of Patients with Lab Test Done	59	74	578
Hematocrit			
> 20% increase from baseline and ≥ 1.3 x ULN (34.9 ~ 44.5%)	-	-	1 (0.2%)
Leukocytes			
> 30% decrease from baseline and ≤ 0.6 x LLN (3.4 ~ 10.5 x 10^9/L)	-	-	1 (0.2%)
> 25% increase from baseline and > 1.5 x ULN (3.4 ~ 10.5 x 10^9/L)	-	-	1 (0.2%)
Eosinophils (%)			
> 100% increase from baseline and > 3 x ULN (1 ~ 4%)	-	-	1 (0.2%)
Lymphocytes (%)			
> 10% decrease from baseline and < 0.2 x LLN (17 ~ 42%)	-	-	1 (0.2%)
Neutrophils (count)			
> 5% decrease from baseline and < 0.5 x LLN (1.5 ~ 8 x 10^9/L)	2 (3.4%)	2 (2.7%)	2 (0.3%)
> 1.6 x ULN (1.5 ~ 8 x 10^9/L)	-	-	8 (1.4%)
Platelets			
Any decrease from baseline and < 0.6 x LLN (150 ~ 450 x 10^9/L)	-	-	4 (0.7%)
≥ 100% increase from baseline and > 2 x ULN (150 ~ 450 x 10^9/L)	1 (1.7%)	-	-

LLN= Lower limit of normal, ULN= Upper limit of normal

Table 3: Clinically Significant Abnormal Changes in Chemistry Test Findings Reported in Kuvan-Treated Patients

	Controlled Studies		All Kuvan-Treated (n=579)
Parameter Notable Criteria (Reference Ranges)	Placebo (n=59)	Kuvan (n=74)	
No. of Patients with Lab Test Done	59	74	578
Alkaline phosphatase			
Any decrease from baseline and < 0.4 x LLN (138 ~ 511 U/L)	-	-	1 (0.2%)
ALT			
> 20% increase from baseline and > 3 x ULN (0 ~ 45 U/L)	-	-	6 (1.0%)
AST			
> 50% increase from baseline and > 2 x ULN (0 ~ 40 U/L)	1 (1.7%)	-	3 (0.5%)
GGT			
> 10% increase from baseline and > 3 x ULN (6 ~ 37 U/L)	-	1 (1.4%)	3 (0.5%)
Glucose			
< 0.5 x LLN (70 ~ 100 mg/dL)	-	-	1 (0.2%)
LDH			
< 0.1 x LLN (145 ~ 345 U/L)	-	-	1 (0.2%)
Potassium			
> 1.2 x ULN (3.6 ~ 5 mmol/L)	-	1 (1.4%)	3 (0.5%)
Total Bilirubin			
> 5% increase from baseline and > 2.5 x ULN (0.1 ~ 1 mg/dL)	-	-	2 (0.3%)
Total Cholesterol			
> 10% increase from baseline and > 1.25 x ULN (0 ~ 239 mg/dL)	-	-	2 (0.3%)

LLN= Lower limit of normal, ULN= Upper limit of normal

Post Marketing Adverse Drug Reactions
The following adverse reactions have been identified during post-approval use of Kuvan. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish causal relationship to drug exposure.

Eye disorders: eyelid oedema
Gastrointestinal disorders: gastritis, oesophageal pain, oesophageal disorder, dyspepsia, abdominal pain, retching, nausea, vomiting, GERD, and epigastric ulcer
General disorders and administration site conditions: oedema peripheral
Immune system disorders: hypersensitivity, anaphylaxis
Infections and infestations: pharyngitis
Nervous System Disorders: hyperactivity [see OVERDOSAGE], convulsions
Respiratory, thoracic and mediastinal disorders: cough, dyspnoea, oropharyngeal pain, throat tightness
Renal: nephrolithiasis
Skin and subcutaneous tissue disorders: urticaria, rash
Vascular disorders: pallor

DRUG INTERACTIONS

Overview
In vitro:
The potential for sapropterin dihydrochloride to induce or inhibit cytochrome P450 enzymes was evaluated in *in vitro* studies which showed sapropterin did not inhibit CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5, nor induce CYP 1A2, 2B6, or 3A4/5.

An additional in vitro study showed sapropterin did not inhibit OAT1, OAT3, OCT2, MATE1 and MATE2-K transporters. The potential for sapropterin dihydrochloride to inhibit OATP1B1 and OATP1B3 has not been adequately studied. Based on in vitro study, there is potential for sapropterin dihydrochloride to inhibit P-gp and BCRP in the gut at therapeutic doses.

Co-administration of Kuvan may increase systemic exposure to drugs that are substrates for P-gp or BCRP.

In vivo:
No in vivo drug-drug interaction studies have been conducted.

Drug-Drug Interactions

Table 4: Potential Drug-Drug Interactions

Co-administered Drug	Reference	Effect	Clinical comment
Drugs that cause vasodilation, including those administered topically, by affecting nitric oxide (NO) metabolism or action including classical NO donors (e.g. glyceryl trinitrate (GTN), isosorbide dinitrate (ISDN), sodium nitroprusside (SNP), molsidomin), phosphodiesterase type 5 (PDE-5) inhibitors and minoxidil.	Theoretical	Hypotension	Caution is recommended during concomitant use of Kuvan with all medicinal products that cause vasodilation. Monitor blood pressure when administering Kuvan with drugs that affect nitric oxide mediated vasorelaxation (e.g. PDE-5 inhibitors such as sildenafil, vardenafil, or tadalafil). The combined use of these medications has not been evaluated in humans. (see WARNINGS AND PRECAUTIONS)
Drugs known to affect folate metabolism (e.g. methotrexate) and their derivatives	Theoretical	Decrease of BH4 levels by inhibiting the enzyme dihydropteridine reductase (DHPR)	Caution should be used with the administration of Kuvan to patients who are receiving drugs that are known to affect folate metabolism. (see WARNINGS AND PRECAUTIONS)
Levodopa	Case Study (post-marketing)	Convulsions, exacerbation of convulsions, over-stimulation, or irritability	Caution should be used with the administration of Kuvan to patients who are receiving levodopa. (see WARNINGS AND PRECAUTIONS)
Drugs that are substrates for P-gp (e.g. Digoxin) or BCRP (e.g. Rosuvastatin).	*In vitro* study	Co-administration of Kuvan may increase systemic exposure to drugs that are substrates for P-gp or BCRP	Caution should be used with the administration of Kuvan to patient who are concomitantly receiving P-gp or BCRP substrates.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Response to treatment cannot be accurately pre-determined by laboratory testing alone (e.g. molecular testing), and can only be determined by a therapeutic trial of Kuvan. Response to treatment is determined by a decrease in blood phenylalanine following treatment with Kuvan. A satisfactory response is defined as a ≥30 percent reduction in blood phenylalanine levels or attainment of the therapeutic blood phenylalanine goals defined for an individual patient by the treating physician.

The recommended starting dose of Kuvan is 10 mg/kg taken once daily.

Response to therapy is determined by change in blood Phe following treatment with Kuvan at 10 mg/kg/day for a period of up to 1 month. Blood Phe levels should be checked after 1 week of Kuvan treatment and periodically for up to a month. If blood Phe does not decrease from baseline at 10 mg/kg/day, the dose may be increased weekly to a maximum of 20 mg/kg/day, with frequent monitoring of blood Phe levels over a one month period. Patients whose blood Phe does not decrease after 1 month of treatment at 20 mg/kg/day are considered non-responders, and treatment with Kuvan should be discontinued in these patients. Once responsiveness to Kuvan has been established, the dosage may be adjusted within the range of 5 to 20 mg/kg/day according to response to therapy. Doses of Kuvan above 20 mg/kg/day have not been evaluated for efficacy and safety in clinical trials.

Periodic blood Phe monitoring is recommended to assess blood Phe control.

Treatment with Kuvan may decrease blood phenylalanine levels below the desired therapeutic level. Adjustment of the Kuvan dose or modification of dietary phenylalanine intake may be required to achieve and maintain blood phenylalanine levels within the desired therapeutic range.

Monitoring

As recommended for clinical management of PKU, blood Phe levels in patients receiving Kuvan should be tested one or two weeks after each dose adjustment and monitored frequently thereafter [1]. Patients treated with Kuvan must continue on a restricted phenylalanine diet.

Missed Dose

A missed dose should be taken as soon as possible, but 2 doses should not be taken on the same day.

Administration

For PKU, Kuvan should be administered orally with a meal to increase absorption, and preferably at the same time each day. When Kuvan is taken with a high fat, high calorie meal, the absorption of the drug increases by 30 – 80% [see Pharmacokinetics].

For administration to adults and children weighing more than 10 kg, Kuvan tablets can be swallowed as whole tablets or dissolved in 120 – 240 mL (4 to 8 oz) of water or apple juice and

taken within 15 minutes of dissolution. To make the tablets dissolve faster, tablets may be stirred or crushed. The tablets may not dissolve completely and patients may see small pieces floating on top of the water or apple juice. If after drinking the medicine, patients still see pieces of the tablet in the container, more water or apple juice can be added to make sure all of the medicine is consumed. Kuvan tablets may also be crushed and then mixed in a small amount of soft foods such as apple sauce or pudding and consumed within 15 minutes of mixing.

For children one month of age and older weighing up to 20 kg, who are unable to safely swallow whole tablets, the tablets can be crushed and dissolved in water or apple juice based on the dosing information provided in Table 5 and 6. A portion of this solution corresponding to the required dose may then be administered orally via an oral dosing syringe. Table 5 provides dosing information at the recommended starting dose of 10 mg/kg per day. Refer to Table 6 for dosing information at 20 mg/kg per day if dosage adjustment is needed. The solution should be consumed within 15 minutes of dissolution.

Table 5: 10 mg/kg per day Dosing Table for Children Weighing up to 20 kg

Weight (kg)	Dose (mg/kg/day)	Total dose (mg/day)	Volume of dissolution (ml)‡	Number of tablets to be dissolved*	Volume of solution to be administered (ml)
3	10	30	20	1	6
3.5	10	35	20	1	7
4	10	40	20	1	8
4.5	10	45	20	1	9
5	10	50	20	1	10
5.5	10	55	20	1	11
6	10	60	20	1	12
6.5	10	65	20	1	13
7	10	70	20	1	14
7.5	10	75	20	1	15
8	10	80	20	1	16
8.5	10	85	20	1	17
9	10	90	20	1	18
9.5	10	95	20	1	19
10	10	100	20	1	20
11	10	110	40	2	22
12	10	120	40	2	24
13	10	130	40	2	26
14	10	140	40	2	28
15	10	150	40	2	30
16	10	160	40	2	32
17	10	170	40	2	34
18	10	180	40	2	36
19	10	190	40	2	38
20	10	200	40	2	40

*Starting dose for infants is 10 mg/kg per day. Dosing information for 20 mg/kg per day is provided in Table 6.
‡ Volume of water or apple juice to dissolve Kuvan tablets. After the volume to be administered is drawn, the remaining mixture should be discarded and the solution should not be used beyond 15 minutes.

Table 6: 20 mg/kg per day Dosing Table for Children Weighing up to 20 kg

Weight (kg)	Dose (mg/kg/day)	Total dose (mg/day)	Volume of dissolution (ml)[†]	Number of tablets to be dissolved[*]	Volume of solution to be administered (ml)
3	20	60	20	1	12
3.5	20	70	20	1	14
4	20	80	20	1	16
4.5	20	90	20	1	18
5	20	100	20	1	20
5.5	20	110	40	2	22
6	20	120	40	2	24
6.5	20	130	40	2	26
7	20	140	40	2	28
7.5	20	150	40	2	30
8	20	160	40	2	32
8.5	20	170	40	2	34
9	20	180	40	2	36
9.5	20	190	40	2	38
10	20	200	40	2	40
11	20	220	60	3	44
12	20	240	60	3	48
13	20	260	60	3	52
14	20	280	60	3	56
15	20	300	60	3	60
16	20	320	80	4	64
17	20	340	80	4	68
18	20	360	80	4	72
19	20	380	80	4	76
20	20	400	80	4	80

[†] Volume of water or apple juice to dissolve Kuvan tablets. After the volume to be administered is drawn, the remaining mixture should be discarded and the solution should not be used beyond 15 minutes.

OVERDOSAGE

Two unintentional overdoses with Kuvan have been reported. In one of the reported overdoses with Kuvan, an adult subject participating in a 26-week study received a single dose of 4500 mg (36 mg/kg) instead of 2600 mg (20 mg/kg) in Week 16 of the study. The subject reported mild headache and mild dizziness after taking the dose; both symptoms resolved within one hour with no treatment intervention. Results from liver function laboratory tests obtained immediately following the event were within normal limits. The subject suspended therapy for 24 hours and then restarted Kuvan with no reports of abnormal signs or symptoms. In postmarketing, one pediatric patient received Kuvan doses of 45 mg/kg per day instead of 20 mg/kg per day. The patient reported hyperactivity that began at an unspecified time after overdose and resolved after the Kuvan dose was reduced to 20 mg/kg per day. Patients should be advised to notify their physicians in cases of overdose.

Upper abdominal pain has also been reported after the administration of sapropterin dihydrochloride above the recommended maximum dose of 20 mg/kg/day.

A dose-dependent shortening of the QT interval and increase in heart rate was observed in a study with a single supra-therapeutic dose of 100 mg/kg (5 times the maximum recommended dose).

Treatment of overdose should be directed to symptoms.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Kuvan is a synthetic formulation of BH4, the cofactor for the enzyme phenylalanine hydroxylase (PAH). PAH hydroxylates Phe through an oxidative reaction to form tyrosine. In patients with PKU, PAH activity is absent or deficient. Treatment with BH4 can activate residual PAH enzyme, improve the oxidative metabolism of Phe, and decrease Phe levels in some patients.

Pharmacodynamics

In PKU patients who are responsive to BH4 treatment, blood Phe levels decrease within 24 hours after a single administration of sapropterin dihydrochloride, although maximal effect on Phe level may take a month or longer, depending on the patient [2]. A single daily dose of Kuvan is adequate to maintain stable blood Phe levels over a 24-hour period. Twelve BH4 responsive patients reduced their blood Phe levels within the range of 516 to 986 µmol/L (mean 747 ± 152.6 µmol/L), and maintained their blood Phe levels over a 24-hour period following a daily morning dose of 10 mg/kg/day. The blood Phe level remained stable during a 24-hour observation period. No substantial increases in blood Phe levels were observed following food intake throughout the 24-hour period.

Effects of Kuvan on the QTc interval

A randomized, placebo- and active-controlled, 4-period crossover ECG assessment study was performed in 56 healthy adult subjects. The subjects received single 20 mg/kg and 100 mg/kg oral doses of sapropterin. At the therapeutic 20 mg/kg dose, sapropterin was associated with statistically significant QTc ($QT/RR^{0.37}$) shortening at 3 and 6 hours post-dosing, with a maximum mean difference from placebo of -2.6 (90% CI -4.6, -0.6) ms at 3 h post-dosing. At the supratherapeutic 100 mg/kg dose, statistically significant QTc shortening was observed from 2 to 6 hours, inclusive, and at 10 h with a maximum mean difference from placebo of -8.2 (90% CI -10.4, -6.0) ms at 4.5 h post-dosing.

At the therapeutic 20 mg/kg dose, sapropterin had no effect on heart rate. At the supratherapeutic 100 mg/kg dose, heart rate was significantly increased from 3 to 4.5 h post-

dosing, with a maximum mean difference from placebo of 4.0 (90% CI 2.8, 5.2) bpm at 3.5 h post-dosing. The clinical relevance of the data has not been established.

Pharmacokinetics

Absorption
Studies in healthy volunteers have shown comparable absorption of sapropterin dihydrochloride when tablets are dissolved in water or orange juice and taken under fasted conditions. Administration of dissolved tablets after a high-fat/high-calorie meal resulted in mean increases in C_{max} of 84% and AUC of 87% (dissolved in water). However, there was extensive variability in individual subject values for C_{max} and AUC across the different modes of administration and meal conditions. In the clinical trials of Kuvan, drug was administered in the morning as a dissolved tablet without regard to meals. There was little evidence to suggest drug accumulation at the highest daily dose (20 mg/kg).

Table 7: Summary of Kuvan's Pharmacokinetic Parameters in healthy subjects when administered under fed conditions either dissolved in water or swallowed intact

	C_{max} (ng/mL)	**$t_{½}$ (hr)**	**T_{max} (hr) (range)**	**AUC_{0-t}**
Study PKU-005 100 mg Tablet orally 10 mg/kg Fed condition Dissolved in water	99.4 ± 38.8	2.97 ± 0.84	5 (3-6)	557 ± 169
Study PKU-009 100 mg Tablet orally 10 mg/kg Fed condition Tablet swallowed intact	121 ± 33.6	4.28 ± 2.79	4.0 (1-5)	709 ± 221
Study PKU-013 100 mg Tablet orally Fed condition Tablet swallowed intact	105 ± 32.1	2.80 ± 1.05	4.5 (2-5)	752 ± 307

Study PKU-013, in healthy adults treated with 10 mg/kg of Kuvan, demonstrated that absorption via intact tablet administration was 40% greater than via dissolved tablet administration under fasted conditions based on AUC_{0-t}. The administration of intact tablets under fed conditions resulted in an approximately 43% increase in the extent of absorption compared to fasted conditions based on AUC_{0-t}.

Absolute bioavailability or bioavailability for humans after oral administration is not known.

Population pharmacokinetic analyses of sapropterin including patients from 1 month to 49 years of age showed that body weight is the only covariate substantially affecting clearance or distribution volume, thereby supporting weight-based dosing (see Table 8). Pharmacokinetics in patients < 1 month and > 49 years of age have not been studied.

Table 8: Apparent Plasma Clearance by Age

Parameter	0 to <1 yr* (N=10)	1 to <6 yr* (N=57)	6 to <12 yr† (N=23)	12 to <18 yr† (N=24)	≥18 yr† (N=42)
CL/F (L/hr/kg) Mean ± SD (Median)	81.5 ± 92.4 (53.6)	50.7 ± 20.1 (48.4)	51.7 ± 21.9 (47.4)	39.2 ± 9.3 (38.3)	37.9 ± 20.2 (31.8)

*Evaluated at 20 mg/kg per day dose
†Evaluated at 5, 10, or 20 mg/kg per day doses

Distribution
In human plasma (in vitro), the protein-binding rate remained constant (22%–34%) within the concentration range of endogenous levels (approximately 3-10 ng/mL). However, when the level exceeded 50 ng/mL, the plasma protein-binding rate decreased to 10% or lower.

Metabolism
Sapropterin is a synthetic form of tetrahydrobiopterin (BH4) and is expected to be metabolized and recycled by the same endogenous enzymes. In vivo endogenous BH4 is converted to quinoid dihydrobiopterin and is metabolized to dihydrobiopterin and biopterin. The enzymes dihydrofolate reductase and dihydropteridine reductase are responsible for the metabolism and recycling of BH4.

Excretion
The mean elimination half-life in PKU patients was approximately 6.7 hours (range 3.9 to 17 hr), comparable with values seen in healthy subjects (range 3.0 to 5.3 hr).

Special Populations and Conditions

Pediatrics (less than 16 years of age):
Pediatric patients with PKU, ages 1 month to 16 years, have been treated with Kuvan in clinical studies [see CLINICAL TRIALS]. The efficacy and safety of Kuvan have not been established in children less than 1 month of age.

Children younger than 7 years and infants less than one year of age treated with Kuvan are at increased risk for low levels of blood Phe compared with older children. Frequent blood monitoring is recommended in the pediatric population to ensure adequate blood Phe level control. See Hypophenylalaninemia.

Geriatrics (65 years and older): Clinical studies of Kuvan in patients with PKU did not include patients aged 65 years and older. It is not known whether these patients respond differently to Kuvan than younger patients. Caution must be exercised when prescribing to geriatric patients.

Gender
The pharmacokinetics of Kuvan were not affected by gender.

Race
The pharmacokinetics of Kuvan were not affected by race.

Hepatic Impairment
Patients with liver impairment have not been evaluated in clinical trials with Kuvan. Monitor liver function tests in patients with liver impairment who are receiving Kuvan because hepatic damage has been associated with impaired Phe metabolism (**See WARNINGS AND PRECAUTIONS**).

Renal Impairment
Patients with renal impairment have not been evaluated in clinical trials. Monitor patients who have renal impairment carefully when they are receiving Kuvan (**See WARNINGS AND PRECAUTIONS**).

Genetic Polymorphism
The influence of genetic polymorphisms on the pharmacokinetics of Kuvan has not been studied.

STORAGE AND STABILITY
Store at 20°C - 25°C; excursions allowed between 15°C - 30°C [See USP Controlled Room Temperature]. Keep container tightly closed. Protect from moisture.

DOSAGE FORMS, COMPOSITION AND PACKAGING
Kuvan® Tablets are unscored, uncoated, immediate-release tablets for oral use. Each tablet contains 100 mg of sapropterin dihydrochloride (equivalent to 76.8 mg of sapropterin base). Tablets are round, off-white to light yellow, mottled, and debossed with '177'.

Each tablet contains the following inactive ingredients: ascorbic acid (USP), crospovidone (NF), dibasic calcium phosphate (USP), D-mannitol (USP), riboflavin (USP), and sodium stearyl fumarate (NF).

Kuvan is supplied in high-density polyethylene bottles, sealed with aluminized film, and closed with child resistant caps. Each bottle contains 120 tablets, a silica gel desiccant cartridge, and a pharmaceutical-grade polyester coil.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

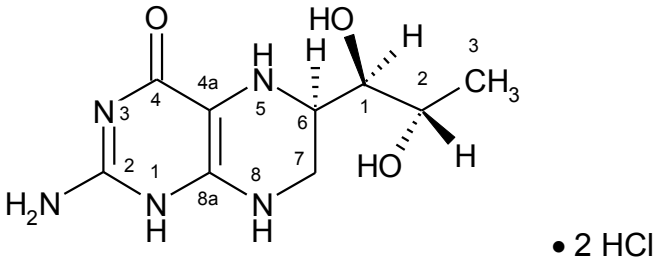
Drug Substance

Proper name: sapropterin dihydrochloride

Chemical name: (6R)-2-amino-6-[(1R,2S)-1,2-dihydroxypropyl] 5,6,7,8-tetrahydro-4(1H)-pteridinone Dihydrochloride

Molecular formula and molecular mass: $C_9H_{15}N_5O_3 \cdot 2HCl$
314.17

Structural formula:



• 2 HCl

Physicochemical properties:

Sapropterin dihydrochloride, the active pharmaceutical ingredient in Kuvan, is a synthetic preparation of the dihydrochloride salt of naturally occurring tetrahydrobiopterin (BH4). Sapropterin dihydrochloride is an off-white to light yellow crystal or crystalline powder. Sapropterin dihydrochloride is very soluble in water, is only slightly soluble in methanol and ethanol, and is practically insoluble in other organic solvents. It melts (with decomposition) at 231-241 °C. Several polymorphic forms have been identified; however, the drug substance is manufactured as a single, stable anhydrous polymorph.

CLINICAL TRIALS

PKU Study Demographics and Trial Design

Table 9: Summary of Patient Demographics and Trial Design in Controlled PKU Studies

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
PKU-003	Multicenter, Multinational, Randomized, Double-blind, Placebo-controlled	Kuvan at 10 mg/kg or placebo, orally, once daily for 6 weeks	PKU patients (n = 88) 41 on Kuvan 47 on placebo	20 years (8 to 49 years)	51 M/37 F
PKU-006	Multicenter, Randomized, Double-blind, Placebo-controlled	Kuvan at 20 mg/kg or placebo, orally, once daily for 6 weeks	PKU patients (n = 45) 33 on Kuvan 12 on placebo	8 years (4 to 12 years)	26 M/19 F

Table 10: Summary of Patient Demographics and Trial Design in Open-label PKU Studies

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
PKU-001	Multicenter, Open-label	Kuvan at 10 mg/kg, orally, once daily for 8 days	PKU patients (n = 489)	22 years (8 to 48 years)	235 M/ 254 F
PKU-004	Multicenter, Open-label	Kuvan at 5, 10 or 20 mg/kg, orally, once daily for 22 weeks	PKU patients (n = 80)	20 years (8 to 49 years)	47 M/33 F
PKU-008	Multicenter, Open-label, Extension study	Kuvan within a range of 5 to 20 mg/kg (starting at last prescribed dose in PKU-004 and at 20 mg/kg from PKU-006), orally, once daily for 3 years, or until Kuvan was commercially available	PKU patients (n = 111)	16 years (4 to 50 years)	67 M/44 F
SPARK	Multicenter, Open-label, randomized, controlled	Kuvan 10 mg/kg/day to 20 mg/kg/day orally for 26 weeks	PKU patients (n=56)	21 months (2 months to 3 years)	30 M/26 F
PKU-015	Multicenter, Open-label, uncontrolled	Kuvan 20 mg/kg orally once daily for 6 months.	PKU patients (n=65)	3.11 years (1 month to 6 years)	25 M/40 F

Study Results in Controlled and Open-label PKU Studies
The efficacy and safety of Kuvan were evaluated in 6 clinical studies in patients with PKU.

PKU-001 was a multicenter, open-label, uncontrolled clinical trial of 489 patients with PKU, ages 8 to 48 years (mean 22 years), who had baseline blood Phe levels ≥ 450 µmol/L and who were not on Phe-restricted diets [4]. All patients received treatment with Kuvan 10 mg/kg/day for 8 days. For the purposes of this study, response to Kuvan treatment was defined as a ≥ 30% decrease in blood Phe from baseline. At Day 8, 96 patients (20%) were identified as responders.

PKU-003 was a multicenter, double-blind, placebo-controlled study of 88 patients with PKU who responded to Kuvan in the PKU-001 study [5]. After a washout period from PKU-001, patients were randomized equally to either Kuvan 10 mg/kg/day (N=41) or placebo (N=47) for 6

weeks. Efficacy was assessed by the mean change in blood Phe level from baseline to Week 6 in the Kuvan-treated group as compared to the mean change in the placebo group.

The results showed that at baseline, the mean (±SD) blood Phe level was 843 (±300) μmol/L in the Kuvan-treated group and 888 (±323) μmol/L in the placebo group. At Week 6, the Kuvan-treated group had a mean (±SD) blood Phe level of 607 (±377) μmol/L, and the placebo group had a mean blood Phe level of 891 (±348) μmol/L. At Week 6, the Kuvan- and placebo-treated groups had mean changes in blood Phe level of –239 and 6 μmol/L, respectively (mean percent changes of –29% (±32) and 3% (±33), respectively). The difference between the groups was statistically significant ($p < 0.001$) (Table 11).

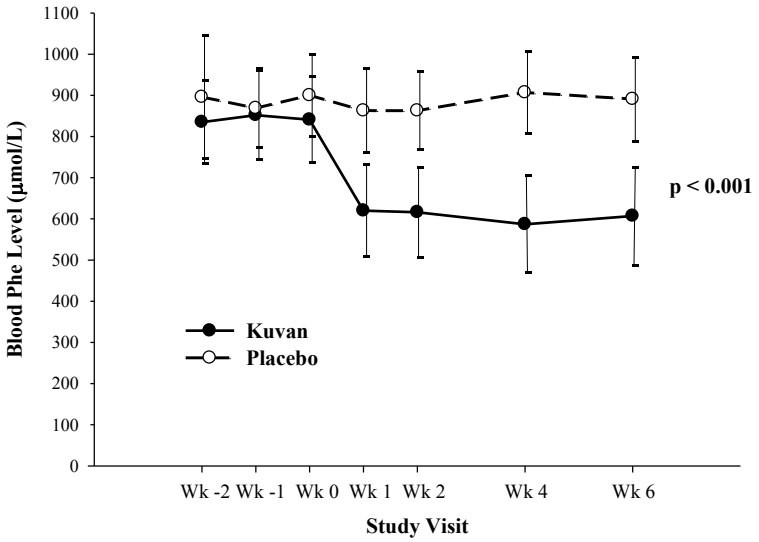
Table 11: PKU-003 Blood Phe Results

	Kuvan (N=41)	**Placebo (N=47)**
Baseline Blood Phe Level[1] (μmol/L)		
Mean (±SD)	843 (±300)	888 (±323)
Percentiles (25^{th}, 75^{th})	620, 990	618, 1141
Week 6 Blood Phe Level (μmol/L)		
Mean (±SD)	607 (±377)	891 (±348)
Percentiles (25^{th}, 75^{th})	307, 812	619, 1143
Mean Change in Blood Phe From Baseline to Week 6 (μmol/L)		
Adjusted Mean (±SE)[2]	-239 (±38)	6 (±36)
Percentiles (25^{th}, 75^{th})	-397, -92	-96, 93
Mean Percent Change in Blood Phe From Baseline to Week 6		
Mean (±SD)	- 29 (±32)	3 (±33)
Percentiles (25^{th}, 75^{th})	-61, -11	-13, 12

[1]The mean baseline (BL) levels shown in this table represent the mean of 3 pretreatment levels (Wk -2, Wk-1, and Wk 0). Treatment with Kuvan or placebo started at Wk 0.
[2]p-value < 0.001, adjusted mean and standard error from an ANCOVA model with change in blood Phe level from baseline to Week 6 as the response variable, and both treatment group and baseline blood Phe level as covariates.

Change in blood Phe was noted in the Kuvan-treated group at Week 1 and was sustained through Week 6 (Figure 1).

Figure 1: Mean Blood Phenylalanine (Phe) Level Over Time[1]



[1]Error bars indicate 95% confidence interval.
Note: Patients began Kuvan or Placebo at Week 0.

PKU-004 was a two-part, multicenter, open-label, extension study of 80 patients with PKU who responded to Kuvan treatment in study PKU-001 and completed participation in study PKU-003. In part 1, patients underwent 6 weeks of forced dose-titration with 3 consecutive 2-week courses of Kuvan at doses of 5, then 20, and then 10 mg/kg/day [6]. Blood Phe level was monitored after 2 weeks of treatment at each dose level. At baseline, mean (±SD) blood Phe was 844 (±398) µmol/L. Results at the end of treatment with 5, 10, and 20 mg/kg/day are presented in Table 12.

Table 12: PKU-004 Blood Phe Results From Forced Dose-Titration

Kuvan Dose Level (mg/kg/day)	No. of Patients	Mean (±SD) Blood Phe Level (µmol/L)	Mean Changes (±SD) in Blood Phe Level From Week 0 (µmol/L)
Baseline (No Treatment)	80	844 (±398)	—
5	80	744 (±384)	-100 (±295)
10	80	640 (±382)	-204 (±303)
20	80	581 (±399)	-263 (±318)

In part 2, patients were assigned a fixed dose of Kuvan for 12 weeks based on their response to the 3 doses given in Part 1. Of the 80 patients in Part 2, 6 (8%) patients received 5 mg/kg/day, 37 (46%) patients received 10 mg/kg/day, and 37 (46%) patients received 20 mg/kg/day. Mean changes (±SD) in blood Phe levels from baseline to Week 22 were -172 (± 391) µmol/L, -176 (± 259) µmol/L and -209 (± 437) µmol/L, respectively.

PKU-006 was a multicenter study of 90 children with PKU, ages 4 to 12 years, who were on Phe-restricted diets and who had blood Phe levels ≤ 480 µmol/L at screening. All patients were treated with open-label Kuvan 20 mg/kg/day for 8 days in part I of the study. Response to Kuvan

was defined as a ≥30% decrease in blood Phe from baseline at Day 8 and a Phe level ≤300 µmol/L. At Day 8, 50 patients (56%) were considered responders to Kuvan [7]. In part 2 of the study, 45 of these PKU children, who responded to Kuvan in part 1 of the study, were then randomized 3:1 to treatment with sapropterin dihydrochloride 20 mg/kg/day (n=33) or placebo (n=12) for ten weeks. After 3 weeks of treatment, blood phenylalanine levels were significantly reduced in the Kuvan group with a mean ± SD decrease from baseline in blood Phe level of 148 ± 134.2 µmol/L ($p<0.001$).

PKU-008 was a multicenter, open-label extension study of 111 patients with PKU who participated in PKU-004 or PKU-006. Doses ranged in this study between 5-20 mg/kg. The mean ± SD exposure to sapropterin for the entire study population was 659 ± 221 days (maximum 953) and 799 + 237 days (maximum 1151) including the previous studies. No new safety signals were seen in this extension study.

Pediatric Population

The safety, efficacy and population pharmacokinetics of Kuvan in children 1 month to < 6 years of age were studied in two open-label studies.

The SPARK (n=56) study is a multicenter, open-label, randomized, controlled study in children aged 2 months to < 4 years old with a confirmed diagnosis of BH4-responsive PKU (defined as having responded to a BH4 test with at least a 30% reduction in Phe levels). Patients were randomized 1:1 to receive either 10 mg/kg/day Kuvan plus a Phe-restricted diet (n=27), or Phe-restricted diet alone (n=29) over a 26-week Study Period.

It was intended that all patients would maintain a blood phenylalanine levels within a range of ≥120 to <360 µmol/L through monitored dietary intake during the 26-week study period. If after approximately 4 weeks, a patient's phenylalanine tolerance had not increased by >20% versus baseline, the Kuvan dose was increased in a single step to 20 mg/kg/day. A 3-year extension period to the study is ongoing.

In SPARK, at the end of the 26-week study period, 25 of 27 subjects in the Kuvan arm were prescribed 10 mg/kg/day and 2 subjects were prescribed 20 mg/kg/day. The results of this study demonstrated that daily dosing with 10 mg/kg/day or 20 mg/kg/day of Kuvan plus Phe-restricted diet led to statistically significant improvements in dietary Phe tolerance compared with dietary Phe restriction alone, while maintaining blood Phe levels within the target range (≥ 120 to < 360 µmol/L). The adjusted mean dietary Phe tolerance in the Kuvan plus Phe-restricted diet group was 80.6 mg/kg/day and was statistically significantly greater ($p < 0.001$) than the adjusted mean dietary Phe tolerance in the Phe-restricted diet-alone group (50.1 mg/kg/day).

PKU-015 is an open label, single arm, multicenter trial in pediatric patients with PKU, aged 1 month to 6 years, who had Phe levels greater than or equal to 360 µmol/L at screening. Part 1 of the study (4 weeks, n=95) was to determine whether subjects were responsive to oral Kuvan dosed at 20 mg/kg/day (defined as a 30% average reduction in blood Phe concentration during the first 4 weeks). During Part 1, Kuvan dose and dietary Phe intake were to remain constant although if blood Phe dropped below 120 µmol/L, Phe supplement could be gradually added to

avoid unstable blood Phe swings. In Part 1, 63 of 95 subjects (66.3%) were Kuvan responders as defined above. Kuvan-responsive subjects in Part 1 who met criteria on age-appropriate cognitive measures could continue to Part 2 of the study. Part 2 is an ongoing a 7-year phase to evaluate neurocognitive function and long-term safety.

In PKU-015, a 6-month substudy that included only Kuvan responders who met criteria on age-appropriate cognitive measures was concurrently conducted with Part 1 and Part 2, to evaluate safety and tolerability. The 6 month substudy included 57 per protocol Kuvan responders plus 8 additional subjects who were considered responders despite not strictly adhering to entry criteria (n=65). During this phase, Kuvan dose could be reduced if the subject did not tolerate 20 mg/kg/day. As well, if blood Phe rose above 240 µmol/L, Phe intake could have been gradually reduced. In the 6 month substudy, the effectiveness of Kuvan alone on reduction of blood Phe levels could not be determined due to concurrent changes in dietary Phe intake. See ADVERSE REACTIONS section for safety results.

DETAILED PHARMACOLOGY

6R-BH4 (tetrahydrobiopterin) is the naturally occurring pteridine, 6R-L-erythro-5,6,7,8 tetrahydrobiopterin (6R-THBP) that is only biochemically active in the enantiomeric R form.

6R-BH4 is an endogenous cofactor for a variety of enzymes, including phenylalanine-4 hydroxylase (PAH). BH4 enhances the function of the mutated PAH enzyme, promoting oxidation of phenylalanine (Phe) to tyrosine, thus lowering blood Phe levels.

Sapropterin dihydrochloride is a synthetic formulation of 6R-BH4, developed as an oral treatment for patients with HPA resulting from PKU. Like naturally occurring BH4, formulations of sapropterin have been shown to enable endogenous PAH and to partially restore oxidative metabolism of Phe, resulting in decreased blood Phe levels in PKU patients [2] [8].

Non-clinical Pharmacokinetics

In animal studies, following administration of Kuvan, bioavailability is approximately 9%. Erythrocyte distribution studies in rats and monkeys revealed that sapropterin distribution was saturable at whole blood concentrations exceeding 250 ng/mL. Studies conducted in rats have shown that sapropterin dihydrochloride does not induce cytochrome P450 activity nor is it metabolized through the cytochrome P450 metabolic pathway (see also Drug Interactions). When 6R-BH4 is used as a cofactor in Phe metabolism, it is converted to pterin 4a-carbinolamine and then to quinoid dihydrobiopterin (R-q-DHBP) and finally reduced back to 6R-BH4. 6R-BH4 is metabolized by the oxidative metabolism of dihydrobiopterin (DHBP) to biopterin (BP). In vivo, BH4 can also be produced by a salvage pathway starting with sepiapterin which is reduced by sepiapterin reductase and dihydrofolate reductase to 6R-BH4 [9]. Sapropterin dihydrochloride and its metabolites are primarily excreted in the feces (75% of a dose) with limited excretion in urine (7% of dose) within 72 hours following oral administration in rats.

Clinical Pharmacodynamics

In PKU patients who are responsive to BH4 treatment, blood Phe levels decrease within 24 hours after a single administration of sapropterin dihydrochloride, although maximal effect on Phe level may take a month or longer, depending on the patient [2]. A single daily dose of

Kuvan is adequate to maintain stable blood Phe levels over a 24-hour period. Twelve BH4 responsive patients reduced their blood Phe levels within the range of 516 to 986 μmol/L (mean 747 ± 152.6 μmol/L), and maintained their blood Phe levels over a 24-hour period following a daily morning dose of 10 mg/kg/day. The blood Phe level remained stable during a 24-hour observation period. No substantial increases in blood Phe levels were observed following food intake throughout the 24-hour period.

Clinical Pharmacokinetics
Studies in healthy volunteers have shown comparable absorption of sapropterin dihydrochloride when tablets are dissolved in water or orange juice and taken under fasted conditions. Administration of an intact tablet under fasted conditions resulted in an average 20% increase in Cmax and AUC relative to dissolved tablets. Administration of a dissolved or intact tablet after a high fat/high calorie meal resulted in increases in Cmax and AUC that ranged from approximately 30% (intact tablet AUC) to 80% (dissolved in water AUC). However, there was extensive variability in individual subject values for Cmax and AUC across the different modes of administration and meal conditions. The mean elimination half-life in PKU patients was approximately 6.7 hours (range 3.9 to 17 hr), comparable with values seen in healthy subjects (range 3.0 to 5.3 hr). There was little evidence to suggest drug accumulation at the highest daily dose (20 mg/kg).

TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility and Developmental Effects
No evidence of carcinogenic effects was observed in mice treated orally with sapropterin dihydrochloride at doses up to 250 mg/kg/day (about the same as the human clinical dose of 20 mg/kg/day, based on body surface area) for 78 weeks; however, the treatment duration of 78 weeks is considered inadequate for a carcinogenicity study. In the 2-year rat carcinogenicity study, at oral doses of sapropterin dihydrochloride of 250 mg/kg/day (about 2 times the human clinical dose of 20 mg/kg/day, based on body surface area) there was a statistically significant increase in the incidence of benign pheochromocytomas in male rats as compared to vehicle-treated rats. A retrospective analysis of the incidence of benign pheochromocytoma in vehicle-treated animals from the same testing facility showed that the incidence observed with sapropterin dihydrochloride in the study was not different than the historical incidence of these tumors in rats treated with vehicle.

Sapropterin dihydrochloride was noted to be weakly positive in the Ames test at concentrations of 625 μg to 5,000 μg/plate. Sapropterin dihydrochloride was positive for producing chromosomal aberrations in Chinese Hamster Lung (with and without metabolic activation) and Chinese Hamster Ovary cells (with metabolic activation), but was negative for chromosomal aberrations in human peripheral blood lymphocytes. Sapropterin dihydrochloride was not mutagenic when assessed in *in vivo* mouse micronucleus tests at doses up to 2000 mg/kg/day.

Sapropterin dihydrochloride was found to have no effect on fertility of male and female rats at oral doses up to 400 mg/kg/day (about 3 times the human clinical dose of 20 mg/kg, based on body surface area).

Reproductive developmental studies have been conducted in rats and rabbits at doses up to 400 mg/kg/day and 600 mg/kg/day, respectively (about 3 times in rats and 10 times in rabbits the human clinical dose of 20 mg/kg/day, based on body surface area). No evidence of teratogenic effects has been observed in either species. In rabbits, there was a non-statistically significant increase in the incidence of holoprosencephaly at the 600 mg/kg/day dose. Placental migration of sapropterin dihydrochloride to the fetuses was not seen in rats dosed orally at 10 mg/kg/day during pregnancy.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

KUVAN®
sapropterin dihydrochloride tablets

Read this carefully before you start taking Kuvan and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Kuvan.

What is Kuvan used for?
Kuvan is used in combination with a phenylalanine (Phe)-restricted diet to reduce blood Phe levels in patients with high blood Phe levels due to tetrahydrobiopterin (BH4)-responsive Phenylketonuria (PKU). An enzyme in your body, phenylalanine hydroxylase (PAH), helps break down Phe, an amino acid found in food. This enzyme does not work right or is not present in patients with this disease. PKU can lead to high blood Phe levels in most patients. High blood Phe levels are toxic to the brain and can lead to lower intelligence and decrease in the ability to focus, remember, and organize information.

How does Kuvan work?
Kuvan activates an enzyme in the body called PAH to help reduce the blood Phe levels in some patients with PKU. The blood Phe levels must be monitored to see if Kuvan is working.

It is not possible to know whether or not Kuvan will work for you until you start taking Kuvan. Your doctor will monitor your blood Phe levels when you start taking Kuvan to see if the drug is working.

What are the ingredients in Kuvan?
Medicinal ingredients: sapropterin dihydrochloride
Non-medicinal ingredients: Ascorbic acid, crospovidone, dibasic calcium phosphate, D-mannitol, riboflavin, and sodium stearyl fumarate.

Kuvan comes in the following dosage forms:
Kuvan Tablets (100 mg) are round, mottled, off-white to light yellow and debossed with "177".

Do not use Kuvan if:
You or your child has ever had an allergic reaction (for example a rash or itchiness) to sapropterin dihydrochloride or any ingredient in this medicine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Kuvan. Talk about any health conditions or problems you may have, including if you:

- Have a fever
- Are pregnant or planning to become pregnant
- Are breast feeding or planning to breast feed
- Have liver or kidney problems
- Have burning sensation or pain in your upper abdomen/stomach
- Have too much or constant activity (hyperactivity, such as fidgeting, moving around too much, or talking too much)
- Have seizures or fits
- Have poor nutrition or have a loss of appetite
- Are taking levodopa, a drug used to treat Parkinson's Disease
- Are taking drugs that affect how your body uses the B vitamin folate (e.g., methotrexate, used for cancer treatment and to treat some immune system disorders) because these drugs could affect how Kuvan works in your body
- Are taking medicines for erectile dysfunction like Viagra (sildenafil), Levitra (vardenafil), or Cialis (tadalafil)
- Are taking any medicines that may lower your blood pressure (e.g., glyceryl trinitrate (GTN), isosorbide dinitrate (ISDN), sodium nitroprusside (SNP), molsidomin, minoxidil)

Other warnings you should know about:
Kuvan should be prescribed by a doctor experienced in the management of PKU. Your doctor and/or healthcare professional will regularly measure your blood Phe and provide nutritional counseling to ensure your blood Phe levels stay in the desirable range. Patients with PKU who are taking Kuvan should also be treated with a Phe-restricted diet and closely monitored for their overall protein intake, because high blood Phe levels with PKU can result in severe neurologic damage.

Some infants under 1 year of age and children under the age of 7 may experience low blood Phe levels.

Not all patients with PKU respond to treatment with Kuvan. Your doctor will continue to monitor your blood Phe levels during your treatment with Kuvan to make sure that your blood Phe levels are not too high or too low.

Kuvan has not been studied in patients less than 1 month of age or 65 years and older therefore it is not known how they will respond to treatment with Kuvan.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Kuvan:

- Levodopa (used to treat Parkinson's disease)

- Medicines for the treatment of cancer (e.g. methotrexate)
- Medicines for treatment of bacterial infections (e.g. trimethoprim)
- Medicines that may lower your blood pressure (e.g. glyceryl trinitrate (GTN), isosorbide dinitrate (ISDN), sodium nitroprusside (SNP), molsidomin, minoxidil)
- Medicines for erectile dysfunction like Viagra (sildenafil), Levitra (vardenafil), or Cialis (tadalafil)
- Digoxin (used to treat heart problems)
- Rosuvastatin (used to reduce fats in the blood)

How to take Kuvan

Take Kuvan exactly as your doctor has told you.

- Take Kuvan once a day with a meal and preferably at the same time each day.
- You can swallow Kuvan whole or you can dissolve Kuvan tablets in 4 to 8 ounces (1/2 to 1 cup) of water or apple juice. You may also crush Kuvan tablets, then mix into a small amount of soft foods such as apple sauce or pudding and eat within 15 minutes of mixing.
- To dissolve the tablets, mix them in water or apple juice, and drink within 15 minutes of dissolution.
    - It may take a few minutes for the tablets to dissolve. To make the tablets dissolve faster, you can stir or crush them.
    - The tablets may not dissolve completely. You may see pieces floating on top of the water or apple juice. This is normal and safe for you to swallow.
    - If you still see pieces of the tablet in the cup after you drink the mixture, you should add more water or apple juice to make sure that you take all of your medicine.

How to give Kuvan tablets to children who weigh 20 kg or less:

- The dose of Kuvan is based on body weight. This will change as your child grows. Your doctor will tell you:
    - the number of Kuvan tablets needed for one dose,
    - the amount of water or apple juice needed to mix one dose of Kuvan, and
    - the amount of the mixture (tablets and water or apple juice) to give your child for their prescribed dose.
- Give your child the prescribed amount of mixture (tablets and water or apple juice) within 15 minutes after mixing. If you are not able to give your child's dose within 15 minutes after mixing, pour the unused medicine into the trash. You will need to mix a new dose.

Supplies needed to mix and give your child's dose of dissolved Kuvan tablets:

- the number of Kuvan tablets needed for one dose
- a small cup of water or apple juice
- a medicine cup with graduation markings at 20, 40, 60 and 80 mL
- a small spoon or clean utensil for mixing
- an oral dosing syringe (graduated in 1 mL divisions) (10 mL syringe for administration of volumes of ≤10 mL or 20 mL syringe for administration of volumes of >10 mL)
- a pill crusher

Ask your pharmacist where to get these supplies if you do not have them.

Step 1: Find a clean, flat work surface.

Step 2: Place a small cup of water or apple juice, the oral dosing syringe, an empty medicine cup, and the pill crusher on your clean, flat work surface (see Figure A).

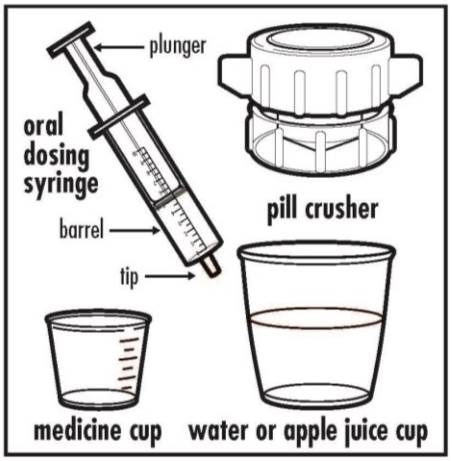

Figure A

Step 3: Pour the appropriate amount (20 mL, 40 mL, 60 mL or 80 mL) of water or apple juice from the small cup into the medicine cup, as instructed by your doctor. Check to make sure that the amount of liquid lines up with the amount that your doctor tells you (see Figure B).

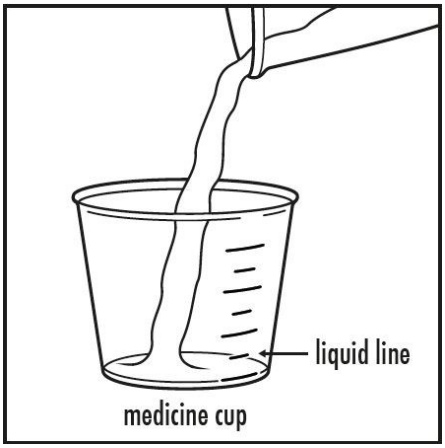

Figure B

Step 4: Use a pill crusher to crush the Kuvan tablet(s). This will make it easier to dissolve the tablet(s). (See Figure C and D).

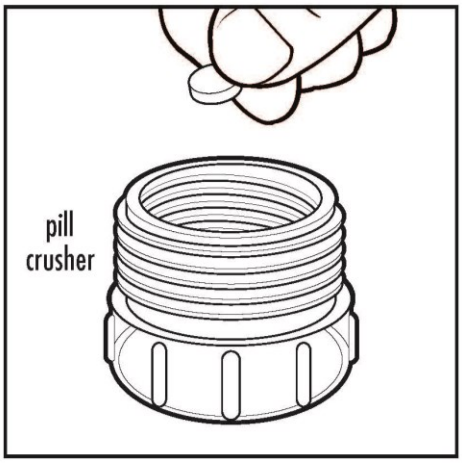

Figure C

and

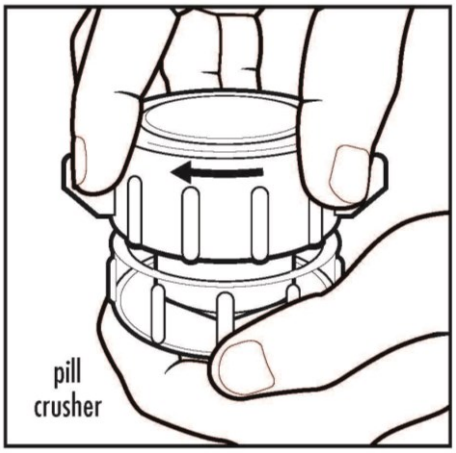

Figure D

Step 5: Place the crushed Kuvan tablet(s) in the medicine cup (see Figure E).

Figure E

Step 6: Stir with the small spoon or other clean utensil until the tablet(s) dissolve (see Figure F). It is normal to see very small pieces of the tablet at the top of the mixture.

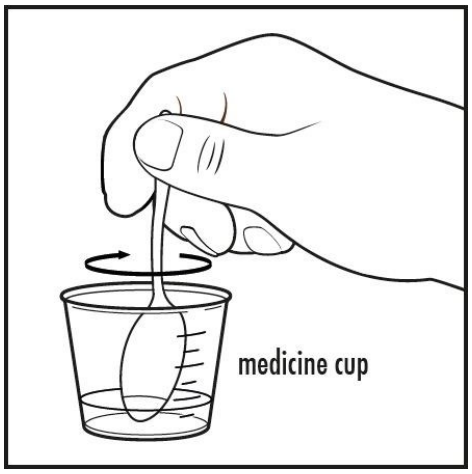

Figure F

Step 7: Place the tip of the oral dosing syringe into the liquid inside the medicine cup. Pull back on the plunger and draw up the amount of the mixture prescribed by your doctor (see Figure G).

Figure G

Step 8: Take the oral dosing syringe out of the medicine cup. Carefully turn the oral dosing syringe so that the tip is pointing up. Check to make sure that the amount of medicine in the oral dosing syringe lines up with the amount of mixture prescribed by your doctor (see Figure H).

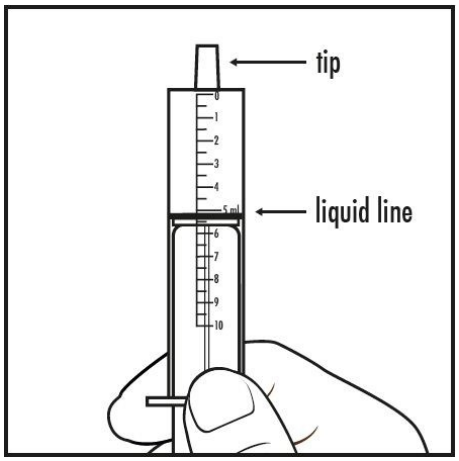

Figure H

Step 9: Place the tip of the oral dosing syringe into your child's mouth. Point the tip of the oral dosing syringe towards either cheek (see Figure I).

Push on the plunger slowly, a small amount at a time, until all of the mixture in the oral dosing syringe is given.

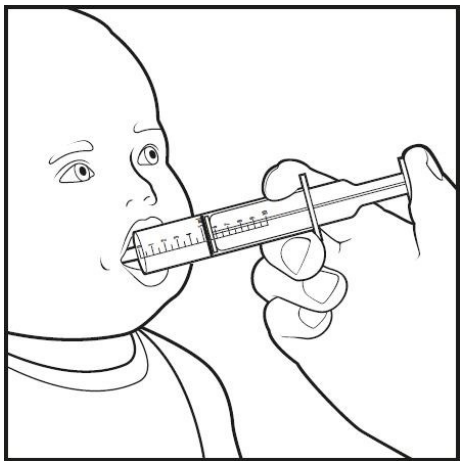

Figure I

Step 10: Throw away any remaining mixture. Remove the plunger from the barrel of the oral dosing syringe. Wash the oral dosing syringe and medicine cup with warm water and air dry. When the oral dosing syringe is dry, put the plunger back into the barrel. Store the oral dosing syringe and medicine cup for the next use.

When you are taking Kuvan, any change you make to your diet may affect your blood Phe level. Follow your doctor's instructions carefully and do not make any changes to your dietary Phe intake before discussing with your doctor. Your doctor will continue to monitor your blood Phe levels during your treatment with Kuvan to make sure that your blood Phe levels are not too high or too low.

If you have a fever, or if you are sick, your blood Phe level may go up. Tell your doctor as soon as possible so they can change your dose of Kuvan to help keep your blood Phe levels in the desired range.

Usual Dose:

- Kuvan starting dose: 10 mg/kg body weight taken once daily with a meal.
- Your doctor can change your dose of Kuvan depending on how you respond to treatment.

Overdose:

Patients who have accidentally taken too much Kuvan reported mild headache, mild dizziness, stomach or belly pain and/or too much or constant activity (hyperactivity).

If you think you have taken too much Kuvan, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take your dose of Kuvan, take it as soon as you remember that day. But if you miss the dose for that day, skip the missed dose, and continue with your scheduled dose the following day. Do not take two doses of Kuvan on the same day.

What are possible side effects from using Kuvan?

These are not all the possible side effects you may feel when taking Kuvan. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Headache
- Runny nose and stuffy nose
- Diarrhea
- Stomach or belly pain
- Upper respiratory tract infection (like a cold)
- Cough
- Throat pain
- Mouth sores
- Vomiting
- Nausea
- Blurred vision
- Anger
- Bedwetting
- Trouble speaking
- Changes in hair colour

Serious side effects and what to do about them				
Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
UNCOMMON	**Fluid accumulation beneath skin of lower limbs**	√		
	Hives: itchy bumpy rash	√		
	Severe allergic reactions: heavy breathing with whistling sound, trouble breathing, coughing, feeling dizzy or faint, turning red, nausea, and rash.			√
	Oesophageal (foodpipe) disorder	√		
	Pale skin	√		
	Retching (gagging)	√		
	Shortness of Breath	√		
	Swelling of Eyelid	√		
	Throat tightness			√
RARE	**Burning sensation or pain in your upper abdomen/stomach**		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect (www.healthcanada.gc.ca/medeffect);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to: 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store in a cool, dry place between 20°C -25°C; excursions allowed between 15°C - 30°C.
- Do not leave Kuvan in hot or humid places, such as your car or bathroom cabinet.
- Keep Kuvan in its original bottle with the cap closed tightly.
- Protect from moisture. Do not remove the desiccant (the small packet included with your tablets). The desiccant absorbs moisture.
- The color of the tablets may change over time, to yellow. This is normal and you can take these tablets.
- Do not keep Kuvan that is out of date, or that you no longer need. Be sure that if you throw any medicine away, it is out of the reach of children.

Keep out of reach and sight of children.

If you want more information about Kuvan:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (www.healthcanada.gc.ca); or by calling 1-877-597-6744.
- For questions, or to report problems, please contact 1-877-597-6744.

This leaflet was prepared by BioMarin Pharmaceutical Inc.

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