PRODUCT MONOGRAPH

PrKuvan™

(sapropterin dihydrochloride)

100 mg Tablets

Enzyme Activator

BioMarin Pharmaceutical (Canada) Inc.
Toronto, ON
Canada M5H 3C2
www.bmrn.com

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[Pr]Kuvan™

(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 4 to 16 years, have been treated with Kuvan in clinical studies [see CLINICAL TRIALS]. The safety and efficacy of Kuvan in pediatric patients less than 4 years of age have not been established in clinical trials. (See WARNINGS AND PRECAUTIONS, Special Populations).

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 behavioral abnormalities. This may occur even if patients are taking Kuvan but not adequately controlling their blood Phe levels within the recommended target range. Neurocognitive outcomes with Kuvan treatment have not been established in long term clinical studies. Conversely, prolonged levels of blood Phe that are too low have been associated with catabolism and protein breakdown. Active management of dietary Phe intake while taking Kuvan is required to ensure adequate Phe control and nutritional balance.

Identify Non-Responders to Kuvan Treatment
Not all patients with PKU respond to treatment with Kuvan. In clinical trials, approximately 20% to 56% of PKU patients responded to treatment with Kuvan [see CLINICAL TRIALS]. Response to treatment cannot be pre-determined by laboratory testing (e.g., genetic testing), and should only be determined by a therapeutic trial of Kuvan [see DOSAGE AND ADMINISTRATION].

Treat All Patients With a Phe-restricted Diet
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.

Cardiovascular

Use with Drugs Known to Affect Nitric Oxide-Mediated Vasorelaxation
Caution should be used with the administration of Kuvan to patients who are receiving drugs that affect nitric oxide mediated vasorelaxation (e.g., PDE-5 inhibitors such as sildenafil, vardenafil, or tadalafil), because both sapropterin dihydrochloride and PDE-5 inhibitors may induce vasorelaxation. The possible additive effect of co-administering sapropterin and PDE-5 inhibitors potentially could lead to a reduction in blood pressure; however, the combined use of these medications has not been evaluated in humans.

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).

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

Monitor for Allergic Reactions
In clinical trials conducted with Kuvan, no severe allergic reactions were observed. The risks and benefits of continued treatment with Kuvan in patients with mild to moderate allergic reactions (such as rash) should be considered.

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 convulsions, exacerbation of convulsions, over-stimulation, or irritability during co-administration of levodopa and sapropterin.

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: Reproduction studies have been performed in rats and rabbits 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; however, in rabbits there was an increase in the incidence, not statistically significant, of holoprosenscephaly 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.

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. 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.

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 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 4 to 16 years, have been treated with Kuvan in clinical studies [see CLINICAL TRIALS]. 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.

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.

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

In clinical trials, a total of 579 PKU patients were administered 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.

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, 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 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, 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.

Less Common Clinical Trial Adverse Drug Reactions (<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

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

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

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

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
Parameter Notable Criteria (Reference Ranges)	Placebo (n=59)	Kuvan (n=74)	Kuvan-Treated (n=579)
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 a 10-year post-approval safety surveillance program in Japan of another formulation of the same active ingredient (sapropterin). This safety surveillance program was conducted in 30 patients, 27 of whom had disorders other than PKU and had an underlying neurologic condition. The most common adverse reactions were convulsions and exacerbation of convulsions in 3 of the non-PKU patients [see **WARNINGS AND PRECAUTIONS**], and increased gamma-glutamyltransferase (GGT) in 2 of the non-PKU patients.

The following spontaneously reported adverse reactions were identified during the post-approval use of Kuvan and were assessed/reported as possibly related to Kuvan use:

Eye disorders: eyelid oedema

Gastrointestinal disorders: retching

General disorders and administration site conditions: oedema peripheral

Immune system disorders: Hypersensitivity

Respiratory, thoracic and mediastinal disorders: cough, dyspnoea, oesophageal disorder, oropharyneal pain, throat tightness

Skin and subcutaneous tissue disorders: urticaria

Vascular disorders: pallor

DRUG INTERACTIONS

Overview

Sapropterin dihydrochloride does not induce cytochrome P450 activity nor is it metabolized through the cytochrome P450 metabolic pathway.

Kuvan (sapropterin dihydrochloride) and drugs that affect nitric-oxide mediated vasorelaxation (e.g., PDE-5 inhibitors such as sildenafil, vardenafil, or tadalafil), can both induce vasorelaxation. The possible additive effect of co-administering sapropterin and PDE-5 inhibitors potentially could lead to a reduction in blood pressure; however, the combined use of these medications has not been evaluated in humans.

In a 10 year post-marketing safety surveillance program for a non-PKU indication using another formulation of the same active ingredient of Kuvan (sapropterin), 3 patients with underlying neurologic disorders experienced convulsions, exacerbation of convulsions, over-stimulation, or irritability during the co-administration of levodopa and sapropterin.

Drug-Drug Interactions

No drug interaction studies have been performed for Kuvan.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

The recommended starting dose of Kuvan is 10 mg/kg/day 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 in clinical trials.

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 food to increase absorption, and preferably at the same time each day. Kuvan tablets can be dissolved in 120 – 224 ml (4 to 8 oz) of water or apple juice and taken within 15 minutes of dissolution.

When Kuvan is taken with a high fat, high calorie meal, the absorption of the drug increases by 30 – 80% [see Pharmacokinetics].

OVERDOSAGE

In the only reported overdosage with Kuvan, a 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 systems 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.

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

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.

Doses beyond 20 mg/kg/day have not been evaluated in clinical studies.

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 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. There is substantial overlap among the different ways of administering Kuvan (intact tablets, dissolved in water, dissolved in orange juice, fasted and fed), results which indicate that the rate and extent of exposure are comparable.

Although there is a trend toward an increase in exposure when Kuvan is administered with a high fat, high calorie meal as noted above, there is substantial overlap in the individual subject values for C_{max} and AUC_{0-t}. Taking into account the safety profile of Kuvan over doses ranging from 5-20 mg/kg/day any increased exposure due to administration with food does not appear to be of clinical significance.

In the clinical trials of Kuvan, drug was administered in the morning as a dissolved tablet before breakfast.

A population pharmacokinetic analysis of sapropterin that included patients between 8 and 49 years of age showed no effect of age on sapropterin dihydrochloride pharmacokinetics. There was an effect of weight on sapropterin dihydrochloride pharmacokinetics thereby supporting weight-based dosing. The mean terminal elimination half-life of Kuvan was

approximately 6.7 hours (range 3.9 to 17 hr) supporting once daily dosing [3]. Pharmacokinetics in patients < 8 years and > 49 years of age have not been studied.

Table 4: 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)	$t_{½}$ (h)	T_{max} (hr) (range)	$AUC_{0-\infty}$
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

Special Populations and Conditions

Pediatrics: A population pharmacokinetic analysis of sapropterin in patients 8 years and older showed no effect of age on sapropterin dihydrochloride pharmacokinetics.

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™ (sapropterin dihydrochloride) 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

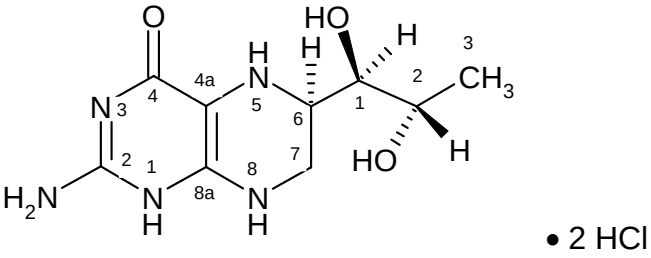
Drug Substance

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:



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 crystals 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 5: 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 6: 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

Study Results in Controlled and Open-label PKU Studies

The efficacy and safety of Kuvan were evaluated in 4 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 7).

Table 7: PKU-003 Blood Phe Results

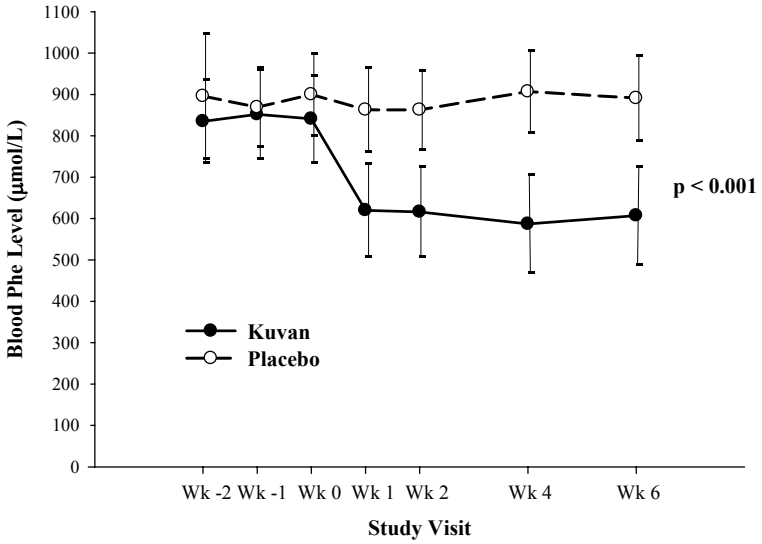
	Kuvan (N=41)	Placebo (N=47)
Baseline Blood Phe Level[1] (μmol/L)		
Mean (±SD)	843 (±300)	888 (±323)
Percentiles (25th, 75th)	620, 990	618, 1141
Week 6 Blood Phe Level (μmol/L)		
Mean (±SD)	607 (±377)	891 (±348)
Percentiles (25th, 75th)	307, 812	619, 1143
Mean Change in Blood Phe From Baseline to Week 6 (μmol/L)		
Adjusted Mean (±SE)[2]	-239 (±38)	6 (±36)
Percentiles (25th, 75th)	-397, -92	-96, 93
Mean Percent Change in Blood Phe From Baseline to Week 6		
Mean (±SD)	- 29 (±32)	3 (±33)
Percentiles (25th, 75th)	-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 8.

Table 8: 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 ($p<0.001$).

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].

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.

Doses beyond 20 mg/kg/day have not been evaluated in clinical studies.

Pharmacokinetics

Absorption: In animal studies, following administration of Kuvan, bioavailability is approximately 9%. In the clinical trials of Kuvan, drug was administered in the morning as a dissolved tablet without regard to meals. 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 C_{max} and AUC relative to dissolved tablets. Administration of a dissolved or intact tablet after a high fat/high calorie meal resulted in increases in C_{max} 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 C_{max} and AUC across the different modes of administration and meal conditions.

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. Erythrocyte distribution studies in rats and monkeys revealed that sapropterin distribution was saturable at whole blood concentrations exceeding 250 ng/mL.

Metabolism: Sapropterin is a dihydrochloride of 6R-BH4, and it cannot be distinguished from endogenous 6R-BH4 in vivo. When 6R-BH4 is used in vivo and recycled 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 can be eliminated 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].

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.

Excretion: Sapropterin dihydrochloride and its metabolites are primarily excreted in the feces (75% of a dose) following oral administration in rats. In rats, about 7% of an orally administered dose appears in the urine within 72 hours. The mean elimination half-life in PKU patients was approximately 6.7 hours (range 3.9 to 17 h), consistent with values seen in healthy subjects. 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; however, in rabbits there was an increase, not statistically significant, in the incidence of holoprosencephaly at the 600 mg/kg/day dose.

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PART III: CONSUMER INFORMATION

^{Pr}Kuvan™
(sapropterin dihydrochloride) Tablets

This leaflet is part III of a three-part "Product Monograph" published when Kuvan was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Kuvan. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Kuvan is used in combination with a Phe-restricted diet to reduce blood phenylalanine (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.

What it does:
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.

Kuvan is a tablet that you can dissolve in water or apple juice.

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.

When it should not be used:
Tell your doctor, if you or your child has ever had an allergic reaction (for example a rash, or itchiness) to Kuvan or any ingredient in this medicine, before you take this medicine.

What the medicinal ingredient is:
sapropterin dihydrochloride

What the important nonmedicinal ingredients are:
Ascorbic acid, crospovidone, dibasic calcium phosphate, D-mannitol, riboflavin, and sodium stearyl fumarate.

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

WARNINGS AND PRECAUTIONS

Kuvan should be prescribed by a doctor experienced in management of PKU. Patients with PKU who are taking Kuvan should also be treated with a Phe-restricted diet, because high blood Phe levels with PKU can result in severe neurologic damage.

Not all patients with PKU respond to treatment with Kuvan. Before you start taking Kuvan, let your doctor know about all of your medical conditions, including if you:

- Have a fever
- Are pregnant or planning to become pregnant
- Are breast feeding
- Have liver or kidney problems
- Are allergic to Kuvan or any other medications
- Have poor nutrition or are anorexic
- Are taking levodopa
- Are taking drugs that inhibit folate metabolism (e.g., methotrexate) 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)

Clinical studies did not include patients aged 65 years and older. The safety and efficacy in patients less than 4 years of age have not been established in clinical trials.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines and herbal and dietary supplements. Kuvan and many other medicines may interact with each other. Your doctor needs to know what medicines you take so he or she can decide if Kuvan is right for you.

Know the medicines you take. Keep a list of your medicines with you to show your doctor. Do not take other medicines while taking Kuvan without first talking to your doctor.

PROPER USE OF THIS MEDICATION

Take Kuvan exactly as your doctor has told you.

- Take Kuvan once a day with food and preferably at the same time each day.
- Kuvan tablets can be dissolved in 4 to 8 ounces (1/2 to 1 cup) of water or apple juice
- 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 after drinking your medicine you still see pieces of the tablet, you should add more water or apple juice to make sure that you take all of your medicine.

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

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.

Overdose:

In the event of a suspected overdose, please contact your health care provider, hospital emergency department or regional poison control centre immediately.

Missed Dose:

If you forget to take your dose of Kuvan, take it as soon as you remember that day. If you miss a day, do not double your dose the next day, just skip the missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects reported when using Kuvan are:

- **Headache**
- **Diarrhoea**
- **Abdominal pain**
- **Upper respiratory tract infection (like a cold)**
- **Throat pain**
- **Vomiting**
- **Nausea**

These are not all the side effects seen with Kuvan. If you are concerned about these or any other side effects you experience while taking Kuvan, ask your doctor or pharmacist for more information.

Be sure to tell your doctor if you have any side effects when you are taking Kuvan.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Cough	√		
	Throat pain	√		
Uncommon	Fluid accumulation beneath skin of lower limbs	√		
	Hives	√		
	Hypersensitivity			√
	Oesophageal disorder (disorder of the gullet)	√		
	Pale skin	√		
	Retching (gagging)	√		
	Shortness of Breath	√		
	Swelling of Eyelid	√		
	Throat tightness			√

HOW TO STORE IT

- 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 dessicant (the small packet included with your tablets). The dessicant 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 Kuvan and all medicines out of the reach of children.**

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to:
    Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada website at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, please contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.kuvan.com or by contacting the sponsor, BioMarin Pharmaceutical (Canada) Inc., at: 1-877-597-6744.

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Novato, CA 94949
USA

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90537 Feucht
Germany

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Toronto, ON, M5H 3C2
Canada