HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use KUVAN safely and effectively. See full prescribing information for KUVAN.

KUVAN (sapropterin dihydrochloride) tablets, for oral use
KUVAN (sapropterin dihydrochloride) powder, for oral solution
Initial U.S. Approval: 2007

----------RECENT MAJOR CHANGES----------

Dosage and Administration, Administration (2.2)	12/2013
Dosage and Administration, Instructions for Use (2.3)	12/2013
Warnings and Precautions (5)	12/2013

----------INDICATIONS AND USAGE----------

Kuvan is a phenylalanine hydroxylase activator indicated to reduce blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin- (BH4-) responsive Phenylketonuria (PKU). Kuvan is to be used in conjunction with a Phe-restricted diet (1).

----------DOSAGE AND ADMINISTRATION----------

- The recommended starting dose of Kuvan is 10 mg/kg/day taken once daily (2.1).
- Doses of Kuvan may be adjusted in the range of 5 to 20 mg/kg taken once daily. Blood Phe must be monitored regularly (2.1).
- Kuvan should be taken orally with food to increase the absorption (2.2).
- Kuvan tablets may be swallowed whole or dissolved in 4 to 8 oz. (120-240 mL) of water or apple juice. Once dissolved, Kuvan should be taken within 15 minutes (2.3).
- Kuvan powder for oral solution should be dissolved in 4 to 8 oz. (120-240 mL) of water or apple juice and consumed within 30 minutes of preparation (2.3.).

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets, 100 mg (3)
- Powder for Oral Solution, 100 mg (3)

----------CONTRAINDICATIONS----------

None (4).

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity reactions including anaphylaxis have occurred (5.1).
- Gastritis was reported in clinical trials. Monitor patients for signs of gastritis (5.2).
- Monitor blood Phe levels during treatment to ensure adequate blood Phe control (5.3).
- Identify non-responders to Kuvan treatment.
  Not all patients with PKU respond to treatment with Kuvan (5.4).
- Treat all patients with a Phe-restricted diet.
  The initiation of Kuvan therapy does not eliminate the need for ongoing dietary management (5.5).
- Monitor liver function tests in patients with hepatic impairment who are receiving Kuvan (5.6).
- Monitor patients when co-administering Kuvan with medications known to inhibit folate metabolism, or with levodopa. Monitor patients for hypotension when co-administering Kuvan with medications known to affect nitric oxide-mediated vasorelaxation (5.7, 5.8, 5.9).
- There have been post-marketing reports of hyperactivity with administration of Kuvan. Monitor patients for hyperactivity (5.10).

----------ADVERSE REACTIONS----------

The most common adverse reactions (incidence ≥4 %) in patients treated with Kuvan are headache, rhinorrhea, pharyngolaryngeal pain, diarrhea, vomiting, cough, and nasal congestion (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact BioMarin Pharmaceutical Inc. at 1-866-906-6100, or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the Full Prescribing Information are not listed

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FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

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

2. DOSAGE AND ADMINISTRATION

2.1 Dosage

The recommended starting dose of Kuvan is 10 mg/kg/day 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 to 20 mg/kg/day. Patients whose blood Phe does not decrease after 1 month of treatment at 20 mg/kg/day are 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.

2.2 Administration

Kuvan is available as tablets and as powder for oral solution. Kuvan should be taken orally with food to increase absorption, preferably at the same time each day. A missed dose should be taken as soon as possible, but 2 doses should not be taken on the same day.

2.3 Instructions for Use

Kuvan Tablets

Kuvan tablets may be swallowed either as whole tablets or dissolved in 4 to 8 oz. (120 to 240 mL) of water or apple juice and taken orally within 15 minutes of dissolution. It may take a few minutes for the tablets to dissolve. To make the tablets dissolve faster, stir or crush them. The tablets may not dissolve completely. Patients may see small pieces floating on top of the water or apple juice. This is normal and safe for patients to swallow. If after drinking the medicine patients still see pieces of the tablet, they can add more water or apple juice to make sure that they take all of the medicine.

Kuvan Powder for Oral Solution

Kuvan powder for oral solution should be dissolved in 4 to 8 oz. (120 to 240 mL) of water or apple juice and taken orally within 30 minutes of dissolution. Empty the contents of the packet(s) in water or apple juice and mix thoroughly. The powder should dissolve rapidly and completely.

3. DOSAGE FORMS AND STRENGTHS

Kuvan tablets are 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".

Kuvan powder for oral solution is available as a unit dose packet containing 100 mg of sapropterin dihydrochloride (equivalent to 76.8 mg of sapropterin base). The powder is off-white to yellow in color.

4. CONTRAINDICATIONS

None.

5. WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions Including Anaphylaxis

Kuvan is not recommended in patients with a history of anaphylaxis to Kuvan. Hypersensitivity reactions, including anaphylaxis and rash, have occurred *[see Adverse Reactions (6.2)]*. 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.

5.2 Gastritis

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

5.3 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. 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. Monitor blood Phe levels during treatment to ensure adequate blood Phe level control. Frequent blood monitoring is recommended in the pediatric population *[see Patient Counseling Information (17.4)]*.

5.4 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 Studies (14.1)]*. Response to treatment cannot be pre-determined by laboratory testing (e.g., genetic testing), and can only be determined by a therapeutic trial of Kuvan *[see Dosage and Administration (2.1)]*.

5.5 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.

5.6 Monitor Patients with 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.

5.7 Monitor Patients when Co-administering Kuvan and Medications Known to Inhibit Folate Metabolism

Co-administering Kuvan with drugs known to affect folate metabolism (e.g., methotrexate) and their derivatives may require more frequent monitoring of blood Phe levels because these drugs can decrease endogenous BH4 levels by inhibiting the enzyme dihydropteridine reductase (DHPR).

5.8 Monitor Patients for Hypotension when Co-administering Kuvan and Drugs Known to Affect Nitric Oxide-Mediated Vasorelaxation

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), because both sapropterin dihydrochloride and PDE-5 inhibitors may induce vasorelaxation. 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. In animal studies, orally administered Kuvan in combination with a PDE-5 inhibitor had no effect on blood pressure.

5.9 Monitor Patients 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. Monitor for change in neurologic status.

5.10 Monitor Patients for Hyperactivity

In the post-marketing safety surveillance program for PKU, 2 patients experienced hyperactivity with administration of Kuvan. Monitor patients for hyperactivity.

6. ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

PKU Clinical Studies

In clinical studies, Kuvan was administered to 579 patients with PKU in doses ranging from 5 to 20 mg/kg/day for lengths of treatment ranging from 1 to 164 weeks. Patients were aged 4 to 50 years old. The patient population was nearly evenly distributed in gender, and approximately 95% of patients were Caucasian.

The most common adverse reactions (≥4% of patients) across all investigational studies (n=579) were headache, rhinorrhea, pharyngolaryngeal pain, diarrhea, vomiting, cough, and nasal congestion.

The data described in Table 1 reflect exposure of 74 patients with PKU to Kuvan at doses of 10 to 20 mg/kg/day for 6 to 10 weeks in 2 double-blind, placebo-controlled clinical trials. The overall incidence of adverse reactions in patients receiving Kuvan was similar to that reported with patients receiving placebo.

Table 1 enumerates adverse reactions occurring in at least 4% of patients treated with Kuvan in the double-blind, placebo-controlled clinical trials described above.

Table 1: Summary of Adverse Reactions Occurring in ≥4% of Patients in Placebo-Controlled Clinical Studies with Kuvan

MedDRA Preferred Term	Treatment	
	Kuvan (N=74)	Placebo (N=59)
	No. Patients (%)	No. Patients (%)
Headache	11 (15)	8 (14)
Rhinorrhea	8 (11)	0
Pharyngolaryngeal pain	7(10)	1 (2)
Diarrhea	6 (8)	3 (5)
Vomiting	6 (8)	4 (7)
Cough	5 (7)	3 (5)
Nasal congestion	3 (4)	0

In open-label, uncontrolled clinical trials in which all patients received Kuvan in doses of 5 to 20 mg/kg/day, adverse reactions were similar in type and frequency to those reported in the double-blind, placebo-controlled clinical trials *[see Clinical Studies (14.1)]*.

In a long term, open-label, extension study of 111 patients receiving Kuvan in doses of ranging from 5 to 20 mg/kg/day *[see Clinical Studies (14.1)]*, adverse reactions were similar in type and

frequency to those reported in the previous clinical studies. Fifty five patients received Kuvan both as dissolved and intact tablets. There were no notable differences in the incidence or severity of adverse reactions between the two methods of administration.

Safety Experience from Clinical Studies for Non-PKU Indications
Approximately 800 healthy volunteers and patients with disorders other than PKU, some of whom had underlying neurologic disorders or cardiovascular disease, have been administered a different formulation of the same active ingredient (sapropterin) in approximately 19 controlled and uncontrolled clinical trials. In these clinical trials, subjects were administered sapropterin at doses ranging from 1 to 100 mg/kg/day for lengths of exposure from 1 day to 2 years. Serious and severe adverse reactions (regardless of causality) during sapropterin administration were convulsions, exacerbation of convulsions *[see Warnings and Precautions (5.9)]*, dizziness, gastrointestinal bleeding, post-procedural bleeding, headache, irritability, myocardial infarction, overstimulation, and respiratory failure. Common adverse reactions were headache, peripheral edema, arthralgia, polyuria, agitation, dizziness, nausea, pharyngitis, abdominal pain, upper abdominal pain, and upper respiratory tract infection.

6.2 Post-Marketing Experience

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.

In worldwide marketing experience, the most common adverse reactions due to Kuvan are oropharyngeal pain, pharyngitis, esophageal pain, gastritis, dyspepsia, abdominal pain, nausea and vomiting. Hypersensitivity reactions including anaphylaxis and rash have been reported. Most hypersensitivity reactions occurred within several days of initiating treatment. Two cases of hyperactivity have been reported, including one case in a patient who received an accidental overdose of Kuvan *[see Warnings and Precautions (5.1, 5.10)]*.

7. DRUG INTERACTIONS

No drug interaction studies were performed.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C
A patient registry has been established that collects data on women who are treated with Kuvan during pregnancy. For more information regarding the registry program call 1-866-906-6100.

Risk Summary
There are no adequate and well-controlled studies with Kuvan in pregnant women. An embryo-fetal development study with sapropterin dihydrochloride in rats using oral doses up to 3 times the maximum recommended human dose (MRHD) given during the period of organogenesis showed no effects. In a rabbit study using oral administration of sapropterin dihydrochloride

during the period of organogenesis, a rare defect, holoprosencephaly, was noted at 10 times the MRHD. Kuvan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Disease-associated maternal and/or embryofetal risk

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 anomalies. Good dietary control of Phe levels during pregnancy is essential to reduce the incidence of Phe-induced teratogenic effects.

Animal Data

No effects on embryo-fetal development were observed in a reproduction study in rats using oral doses of up to 400 mg/kg/day sapropterin dihydrochloride (about 3 times the MRHD of 20 mg/kg/day, based on body surface area) administered during the period of organogenesis. However, in a rabbit reproduction study, oral administration of a maximum dose of 600 mg/kg/day (about 10 times the MRHD, based on body surface area) during the period of organogenesis was associated with a non-statistically significant increase in the incidence of holoprosencephaly in two high dose-treated litters (4 fetuses), compared to one control-treated litter (1 fetus).

8.3 Nursing Mothers

It is not known whether Kuvan is present in human milk. Sapropterin is present in the milk of intravenously, but not orally treated lactating rats. The developmental and health benefits of human milk feeding should be considered along with the mother's clinical need for Kuvan and any potential adverse effects on the human milk-fed child from the drug or from the underlying maternal condition. Exercise caution when Kuvan is administered to a nursing woman.

8.4 Pediatric Use

Pediatric patients with PKU, ages 4 to 16 years, have been treated with Kuvan in clinical studies *[see Clinical Studies (14.1)]*. The safety and efficacy of Kuvan in pediatric patients less than 4 years of age have not been established in clinical studies. Frequent blood monitoring is recommended in the pediatric population to ensure adequate blood Phe level control *[see Patient Counseling Information (17.4)]*.

8.5 Geriatric Use

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 than younger patients.

8.6 Patients with 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.

10. OVERDOSAGE

Two unintentional overdosages with Kuvan have been reported. One adult patient in a Kuvan clinical trial received a single Kuvan dose of 4,500 mg (36 mg/kg) instead of 2,600 mg (20 mg/kg). The patient reported mild headache and mild dizziness immediately after taking the dose; both symptoms resolved within 1 hour with no treatment intervention. There were no associated laboratory test abnormalities. The patient 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/day instead of 20 mg/kg/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/day.

In a clinical study to evaluate the effects of Kuvan on cardiac repolarization, a single supra-therapeutic dose of 100 mg/kg (5 times the maximum recommended dose) was administered to 54 healthy adults. No serious adverse reactions were reported during the study. The only adverse reactions reported in more than 1 subject who received the supra-therapeutic dose were upper abdominal pain (6%) and dizziness (4%). A dose-dependent shortening of the QT interval was observed *[see Clinical Pharmacology (12.2)]*.

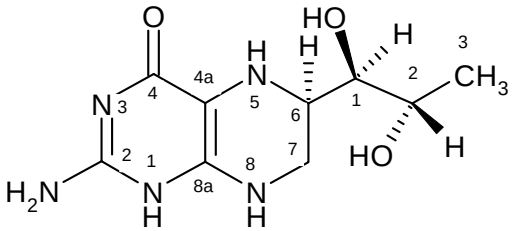
Patients should be advised to notify their physicians in cases of overdose.

11. DESCRIPTION

KUVAN (sapropterin dihydrochloride) is an orally administered Phenylalanine Hydroxylase activator (or PAH activator). 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.

The chemical name of sapropterin dihydrochloride is (6R)-2-amino-6-[(1R,2S)-1,2-dihydroxypropyl]-5,6,7,8-tetrahydro-4(1H)-pteridinone dihydrochloride and the molecular formula is $C_9H_{15}N_5O_3 \cdot 2HCl$ with a molecular weight of 314.17.

Sapropterin dihydrochloride has the following structural formula:



• 2 HCl

Kuvan is supplied as tablets and powder for oral solution containing 100 mg of sapropterin dihydrochloride (equivalent to 76.8mg 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 powder for oral solution is off-white to yellow in color. Each unit dose packet contains the following inactive ingredients: ascorbic acid (USP), D-mannitol (USP), potassium citrate (USP), and sucralose (NF).

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Kuvan is a synthetic form 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 normal oxidative metabolism of Phe, and decrease Phe levels in some patients.

12.2 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 up to a month, depending on the patient. A single daily dose of Kuvan is adequate to maintain stable blood Phe levels over a 24-hour period. Twelve patients with blood Phe levels ranging from 516 to 986 μmol/L (mean 747 ± 153 μmol/L) were assessed with 24-hour blood Phe level monitoring 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 thorough QTc study was performed in 56 healthy adults. This randomized, placebo and active controlled crossover study was conducted to determine if a single supra-therapeutic (100 mg/kg) of Kuvan, or a single therapeutic dose (20 mg/kg) of Kuvan had an effect on cardiac repolarization. In this study, Kuvan was administered after dissolving tablets in water under fed condition. This study demonstrated a dose-dependent shortening of the QT interval. The maximum placebo-subtracted mean change from baseline of the QTc interval was -3.69 and -8.32 ms (lower bound of 90% CI: -5.3 and -10.6 ms) at 20 and 100 mg/kg, respectively.

12.3 Pharmacokinetics

Studies in healthy volunteers have shown comparable absorption of sapropterin 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. 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).

A study in healthy adults with 10 mg/kg of Kuvan demonstrated the 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}.

A population pharmacokinetic analysis of sapropterin including patients between 9 and 49 years of age showed no effect of age on sapropterin pharmacokinetics. Pharmacokinetics in patients <9 years and >49 years of age have not been studied.

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.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 2-year carcinogenicity study was conducted in F-344 rats, and a 78-week carcinogenicity study was conducted in CD-1 mice. In the 104-week oral carcinogenicity study in rats, sapropterin dihydrochloride doses of 25, 80, and 250 mg/kg/day (0.2, 0.7, and 2 times the maximum recommended human dose of 20 mg/kg/day, respectively, based on body surface area) were used. In the 78-week oral carcinogenicity study in mice, sapropterin dihydrochloride doses of 25, 80, and 250 mg/kg/day (0.1, 0.3, and 2 times the recommended human dose, respectively, based on body surface area) were used. In the 2-year rat carcinogenicity study, there was a statistically significant increase in the incidence of benign adrenal pheochromocytoma in male rats treated with the 250 mg/kg/day (about 2 times the maximum recommended human dose, based on body surface area) dose, as compared to vehicle treated rats. The mouse carcinogenicity study showed no evidence of a carcinogenic effect, but the study was not ideal due to its duration of 78 instead of 104 weeks.

Sapropterin dihydrochloride was genotoxic in the *in vitro* Ames test at concentrations of 625 µg (TA98) and 5000 µg (TA100) per plate, without metabolic activation. However, no genotoxicity was observed in the *in vitro* Ames test with metabolic activation. Sapropterin dihydrochloride was genotoxic in the *in vitro* chromosomal aberration assay in Chinese hamster lung cells at concentrations of 0.25 and 0.5 mM. Sapropterin dihydrochloride was not mutagenic in the *in vivo* micronucleus assay in mice at doses up to 2000 mg/kg/day (about 8 times the maximum recommended human dose of 20 mg/kg/day, based on body surface area). Sapropterin dihydrochloride, at oral doses up to 400 mg/kg/day (about 3 times the maximum recommended human dose, based on body surface area) was found to have no effect on fertility and reproductive function of male and female rats.

14. CLINICAL STUDIES

14.1 Clinical Studies in PKU

The efficacy and safety of Kuvan were evaluated in 5 clinical studies in patients with PKU.

Study 1 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. 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.

Study 2 was a multicenter, double-blind, placebo-controlled study of 88 patients with PKU who responded to Kuvan in Study 1. After a washout period from Study 1, 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 2).

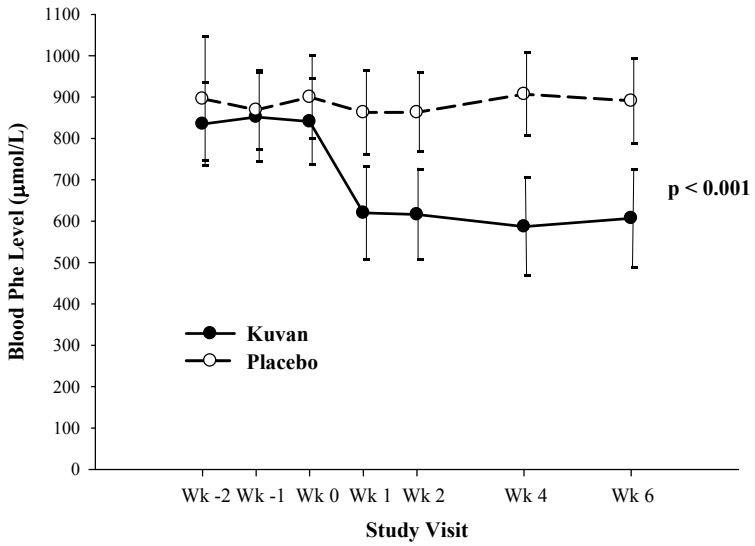
Table 2: Blood Phe Results in Study 2

	Sapropterin (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 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.

Study 3 was a multicenter, open-label, extension study in which 80 patients who responded to Kuvan treatment in Study 1 and completed Study 2 underwent 6 weeks of forced dose-titration with 3 different doses of Kuvan. Treatments consisted of 3 consecutive 2-week courses of Kuvan at doses of 5, then 20, and then 10 mg/kg/day. 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. At the end of treatment with 5, 10, and 20 mg/kg/day, mean (±SD) blood Phe levels were 744 (±384) µmol/L, 640 (±382) µmol/L, and 581 (±399) µmol/L, respectively (Table 3).

Table 3: Blood Phe Results From Forced Dose-Titration in Study 3

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)

Study 4 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. Response to Kuvan was defined as a ≥30% decrease in blood Phe from baseline at Day 8. At Day 8, 50 patients (56%) had a ≥30% decrease in blood Phe.

Study 5 demonstrated the long-term safety of Kuvan in patients with PKU. The study was a multicenter, open-label extension study of 111 patients with PKU who participated in Study 3 or Study 4. Doses ranged in this study between 5-20mg/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.

16. HOW SUPPLIED/STORAGE AND HANDLING

Kuvan tablets, 100 mg, are round, off-white to light yellow, mottled, and debossed with "177". The tablets are supplied as follows:

NDC 68135-300-01 Bottle of 30 tablets
NDC 68135-300-02 Bottle of 120 tablets

Kuvan powder for oral solution, 100 mg, is an off-white to yellow powder. Kuvan powder is packaged in unit dose packets as follows:
NDC 68135-301-22 Carton of 30 unit dose packets
NDC 68135-301-11 Single unit dose packet

Storage
Store Kuvan tablets at 20ºC to 25ºC (68ºF –77ºF); excursions allowed between 15ºC to 30ºC (59ºF –86ºF) [see USP Controlled Room Temperature]. Keep container tightly closed. Protect from moisture.

Store Kuvan powder for oral solution at 20ºC to 25ºC (68ºF –77ºF); excursions allowed between 15ºC to 30ºC (59ºF –86ºF) [see USP Controlled Room Temperature]. Protect from moisture.

Manufactured for:
BioMarin Pharmaceutical Inc.
Novato, CA 94949

17. PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

Patients should be advised of the following information before beginning treatment with Kuvan:

17.1 Important Information to Consider Prior to Prescribing Kuvan

Patients with residual PAH enzyme activity may benefit from taking Kuvan; however, 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.

Since patients have varying degrees of residual PAH enzyme activity and BH4 responsiveness, it is not possible to accurately predict the extent of response before administering Kuvan to the

patient, and response to treatment cannot be pre-determined by laboratory testing (e.g., genetic testing). Response to Kuvan can only be determined by a therapeutic trial.

To determine if a patient may respond to treatment with Kuvan, the patient must be treated with Kuvan and evaluated for changes in blood Phe. Blood Phe levels and dietary Phe intake should be measured frequently *[see Warnings and Precautions (5.3, 5.4)]*.

17.2 Blood Phe Monitoring and Management

Treatment with Kuvan should be directed by physicians knowledgeable in the management of PKU, and the initiation of Kuvan therapy does not eliminate the need for appropriate monitoring by trained professionals. Patients being treated with Kuvan should have frequent blood Phe measurements and nutritional counseling with their physician and other members of the health care team to ensure maintenance of blood Phe levels in the desirable range.

Since changes in dietary Phe intake can obscure the effect of Kuvan on blood Phe levels, and since not all patients will respond to treatment with Kuvan, all patients with PKU should be treated with a Phe-restricted diet in addition to treatment with Kuvan *[see Warnings and Precautions (5.5)]*.

To determine if a patient responds to Kuvan therapy, patients must not modify their existing dietary Phe intake during the evaluation period in order to get an accurate assessment of the effect of Kuvan on blood Phe levels. Baseline blood Phe measurements should be taken just prior to initiation of a Kuvan response test. Patients should be started at a dose of 10 mg/kg/day. Blood Phe levels should be checked after 1 week of Kuvan treatment and periodically for up to a month to determine response. A response to treatment with Kuvan may be determined by a decrease in blood Phe level compared to baseline level. If blood Phe level does not decrease at 10 mg/kg/day, the dose may be increased to 20 mg/kg/day. Patients whose blood Phe does not decrease from baseline after 1 month of treatment at 20 mg/kg/day are non-responders, and treatment with Kuvan should be discontinued in these patients *[see Dosage and Administration (2.1)]*.

For patients who respond to Kuvan treatment, the dosage may be adjusted within the range of 5 to 20 mg/kg/day according to response to therapy.

After the dose of Kuvan has been established, continued active management of dietary Phe intake using medical foods and natural sources of proteins is required to ensure blood Phe control and adequate nutritional balance.

17.3 What Are the Benefits of Taking Kuvan?

Prolonged high blood Phe levels are neurotoxic and lead to impairment of intelligence and other brain functions (such as attentiveness). Reduction of blood Phe levels through dietary control is an important determinant of long-term neurologic outcome in PKU patients, and reduction of blood Phe levels in patients with PKU has been shown to decrease the long-term risk of neurologic injury. It is difficult for many patients to maintain reduced blood Phe, and many patients with PKU experience some degree of neurological impairment despite efforts to maintain dietary Phe control.

Kuvan may help maintain reduced blood Phe levels as an adjunct to a Phe-controlled diet. In clinical trials with Kuvan in patients with PKU, reductions in blood Phe levels were observed in some patients. However, long-term neurologic function in patients with PKU receiving Kuvan for the treatment of elevated blood Phe has not been assessed.

17.4 What Are the Risks of Taking Kuvan?

Hypersensitivity reactions including anaphylaxis and rash have been reported. Most hypersensitivity reactions occurred within several days of initiating treatment. Patients should be informed to seek immediate medical attention for evidence of severe allergic reactions *[see Warnings and Precautions (5.1)]*.

During clinical studies, gastritis was reported as a serious adverse reaction. Patients should be informed to notify their physician for symptoms of severe gastritis *[see Warnings and Precautions (5.2)]*.

Response to Kuvan treatment in PKU patients is variable. Not all patients responded to treatment with Kuvan in clinical trials, and the initiation of Kuvan treatment does not eliminate the need to monitor for adequate blood Phe control. Prolonged elevations in blood Phe levels can result in neurologic impairment. Conversely, levels of blood Phe that are too low may be associated with catabolism and protein breakdown. Therefore, when Kuvan is used in combination with a Phe-restricted diet, patients should be monitored closely to ensure adequate control of blood Phe levels and, if necessary, the dose of Kuvan should be adjusted. Frequent blood monitoring is recommended in the pediatric population. All patients with PKU who are being treated with Kuvan should also be treated with a Phe-restricted diet *[see Warnings and Precautions (5.3, 5.4, 5.5)]*.

Some patients may require additional clinical monitoring while taking Kuvan, including patients with hepatic impairment and patients who are taking Kuvan in combination with drugs that inhibit folate metabolism, drugs that affect nitric oxide-mediated vasorelaxation, and levodopa *[see Warnings and Precautions (5.6, 5.7, 5.8, 5.9)]*.

There have been postmarketing reports of hyperactivity while taking Kuvan. Patients should be informed to notify their physician for symptoms of hyperactivity *[see Warnings and Precautions (5.10)]*. The most common adverse reactions (≥4% of patients) during clinical studies were headache, rhinorrhea, pharyngolaryngeal pain, diarrhea, vomiting, cough, and nasal congestion *[see Adverse Reactions (6.1)]*.

17.5 BioMarin PKU Disease Registry

BioMarin established a product registry for PKU patients that also collect data on women who become pregnant while receiving Kuvan treatment.

PATIENT INFORMATION
Kuvan (COO-van)
(sapropterin dihydrochloride)
Tablets

Kuvan (COO-van)
(sapropterin dihydrochloride)
Powder for Oral Solution

What is Kuvan?

Kuvan is a prescription medicine used to lower blood levels of phenylalanine (Phe), in people with a certain type of Phenylketonuria (PKU). Kuvan is used along with a Phe-restricted diet.

What should I tell my doctor before taking Kuvan?

Before you take Kuvan, tell your doctor if you:

- have a fever
- have liver or kidney problems
- are allergic to sapropterin dihydrochloride or any of the ingredients in Kuvan. See the list of ingredients in Kuvan at the end of this leaflet.
- have poor nutrition or have loss of appetite
- are pregnant or plan to become pregnant.

  Pregnancy Registry: There is a pregnancy registry for women who take Kuvan during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.

- are breastfeeding or plan to breastfeed. It is not known if Kuvan passes into your breast milk. Talk to your doctor about the best way to feed your baby if you take Kuvan.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, herbal, and dietary supplements. Kuvan and other medicines may interact with each other.

Especially tell your doctor if you take:

- a medicine that contains levodopa
- an antifolate medicine
- avanafil (Stendra), sildenafil (Revatio, Viagra), tadalafil (Adcirca, Cialis), vardenafil (Staxyn, Levitra)

Tell your doctor if you are not sure if your medicine is one that is listed above.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take Kuvan?

- Take Kuvan exactly as your doctor tells you. Your doctor should tell you how much Kuvan to take and when to take it.
- Your doctor may change your dose of Kuvan depending on how you respond to treatment.
- Take Kuvan 1 time each day with food. It is best to take Kuvan at the same time each day.
- Kuvan comes as a tablet and powder for oral solution.
  - You can swallow Kuvan tablets whole or dissolve the tablets in water or apple juice before taking.
  - Kuvan powder for oral solution should be dissolved in water or apple juice before taking.
  - See the "Instructions for Use" at the end of this Patient Information leaflet for information about the correct way to dissolve and take a dose of Kuvan tablets or Kuvan powder for oral solution.
- It is not possible to know if Kuvan will work for you until you start taking Kuvan. Your doctor will check your blood Phe levels when you start taking Kuvan to see if the medicine is working.
- During treatment with 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 without first talking with your doctor. Even if you take Kuvan, if your Phe blood levels are not well controlled, you can develop severe neurologic problems.
  - Your doctor should continue to monitor your blood Phe levels often 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.
- If you forget to take your dose of Kuvan, take it as soon as you remember that day. Do not take 2 doses in a day.
- If you take too much Kuvan, call your doctor for advice.

What are the possible side effects of Kuvan?

Kuvan can cause serious side effects, including:

- **Severe allergic reactions.** Stop taking Kuvan and get medical help right away if you develop any of these symptoms of a severe allergic reaction:
  - wheezing or trouble breathing
  - coughing
  - feeling lightheaded or you faint
  - flushing
  - nausea
  - rash

- **Inflammation of the lining of the stomach (gastritis)**. Gastritis can happen with Kuvan and may be severe. **Call your doctor right away if you have any of these signs or symptoms:**
  - severe upper stomach-area (abdominal) discomfort or pain, nausea and vomiting
  - blood in your vomit or stool
  - black, tarry stools

- **Too much or constant activity (hyperactivity) can happen with Kuvan**. Tell your doctor if you have any signs of hyperactivity, including:
  - fidgeting or moving around too much
  - talking too much

The most common side effects of Kuvan are:

- headache
- runny nose and nasal congestion
- sore throat
- diarrhea
- vomiting
- cough

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Kuvan. For more information, ask your doctor or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Kuvan?

- Store Kuvan at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep Kuvan tablets in the 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.

Keep Kuvan and all medicines out of the reach of children.

General information about the safe and effective use of Kuvan

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use Kuvan for a condition for which it was not prescribed. Do not give Kuvan to other people, even if they have the same symptoms you have. It may harm them.

If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about Kuvan that is written for health professionals. For more information, call BioMarin Patient and Physician Support (BPPS) at 1-866-906-6100.

What are the ingredients in Kuvan?

Active ingredient: sapropterin dihydrochloride.

Kuvan tablet inactive ingredients: ascorbic acid, crospovidone, dibasic calcium phosphate, D-mannitol, riboflavin, and sodium stearyl fumarate.

Kuvan powder for oral solution inactive ingredients: ascorbic acid, D-mannitol, potassium citrate, and sucralose.

Instructions for Use

If you are taking Kuvan tablets:

KUVAN tablets can be swallowed whole or dissolved in water or apple juice as follows:

- To dissolve Kuvan tablets, mix them in 4 to 8 ounces (½ to 1 cup) of water or apple juice.
- 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 small pieces floating on top of the water or apple juice. This is normal and safe for you to swallow.
- Drink within 15 minutes.
- After drinking your medicine, if you still see small pieces of the tablet, add more water or apple juice and drink, to make sure that you take all of your medicine.

If you are taking Kuvan powder for oral solution:

- Kuvan powder for oral solution should be dissolved in water or apple juice as follows: To open a packet of Kuvan powder for oral solution, fold and tear or cut at the dotted line in the upper right corner of the packet.
- Empty the contents of the packet into 4 to 8 ounces (1/2 to 1 cup) of water or apple juice.
  The powder should dissolve completely within 15 seconds.
- Drink within 30 minutes.

This Patient Information has been approved by the U.S. Food and Drug Administration.

BIOMARIN®

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