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

----------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----------
Starting dose:
- Patients 1 month to 6 years: The recommended starting dose of Kuvan is 10 mg/kg taken once daily (2.1, 5.3).
- Patients 7 years and older: The recommended starting dose of Kuvan is 10 to 20 mg/kg taken once daily (2.1).

Dose Adjustment:
- 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).
- Instruct patients to take with a meal.
- Swallow tablets whole or after mixing in a small amount of soft foods or dissolving in recommended liquid. Swallow oral solution after mixing powder in a small amount of soft foods or dissolving in recommended liquids.

----------DOSAGE FORMS AND STRENGTHS----------
- Tablets, 100 mg (3)
- Powder for Oral Solution, 100 mg, 500 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).
- Children younger than 7 years treated with Kuvan doses of 20 mg/kg per day are at increased risk for low levels of blood Phe compared with children 7 years and older (5.3).
- Monitor blood Phe levels during treatment to ensure adequate blood Phe control (5.4).
- Identify non-responders to Kuvan treatment:
  Not all patients with PKU respond to treatment with Kuvan (5.5).
- Treat all patients with a Phe-restricted diet:
  The initiation of Kuvan therapy does not eliminate the need for ongoing dietary management (5.6).
- Monitor liver function tests in patients with liver impairment who are receiving Kuvan (5.7).
- 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 (5.8, 5.9, 5.10).
- There have been post-marketing reports of hyperactivity with administration of Kuvan. Monitor patients for hyperactivity (5.11).

----------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: 07/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

1. INDICATIONS AND USAGE
2. DOSAGE AND ADMINISTRATION
2.1 Dosage
2.2 Administration
2.3 Instructions for Use
3. DOSAGE FORMS AND STRENGTHS
4. CONTRAINDICATIONS
5. WARNINGS AND PRECAUTIONS
5.1 Hypersensitivity Reactions Including Anaphylaxis
5.2 Gastritis
5.3 Hypophenylalaninemia
5.4 Monitor Blood Phe Levels During Treatment
5.5 Identify Non-Responders to Kuvan Treatment
5.6 Treat All Patients with a Phe-restricted Diet
5.7 Monitor Patients with Hepatic Impairment
5.8 Monitor Patients when Co-administering Kuvan and Medications Known to Inhibit Folate Metabolism
5.9 Monitor Patients for Hypotension when Co-administering Kuvan and Drugs Known to Affect Nitric Oxide-Mediated Vasorelaxation
5.10 Monitor Patients when Co-administering Kuvan and Levodopa
5.11 Monitor Patients for Hyperactivity
6. ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Post-Marketing Experience
7. DRUG INTERACTIONS
8. USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mother
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Patients with Renal Impairment
10. OVERDOSAGE
11. DESCRIPTION
12. CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13. NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14. CLINICAL STUDIES
14.1 Clinical Studies in PKU
16. HOW SUPPLIED/STORAGE AND HANDLING
17. PATIENT COUNSELING INFORMATION

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

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

Patients 1 month to 6 years: The recommended starting dose of Kuvan is 10 mg/kg taken once daily *[see Warnings and Precautions (5.3)]*.

Patients 7 years and older: The recommended starting dose of Kuvan is 10 to 20 mg/kg taken once daily.

If a 10 mg/kg per day starting dose is used, then response to therapy is determined by change in blood Phe following treatment with Kuvan at 10 mg/kg per 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 per day, the dose may be increased to 20 mg/kg per day. Patients whose blood Phe does not decrease after 1 month of treatment at 20 mg/kg per day are non-responders and treatment with Kuvan should be discontinued in these patients.

If a 20 mg/kg per day starting dose is used, then response to therapy is determined by change in blood Phe following treatment with Kuvan at 20 mg/kg per day for a period of 1 month. Blood Phe levels should be checked after 1 week of Kuvan treatment and periodically during the first month. Treatment should be discontinued in patients who do not respond to Kuvan.

Once responsiveness to Kuvan has been established, the dosage may be adjusted within the range of 5 to 20 mg/kg per day according to response to therapy. Periodic blood Phe monitoring is recommended to assess blood Phe control *[see Warnings and Precautions (5.3, 5.6)]*.

2.2 Administration

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

2.3 Instructions for Use

<u>Kuvan Tablets</u>
Kuvan tablets may be swallowed either as whole tablets or dissolved in 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, tablets may be stirred or crushed. 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 in the container, more water or apple juice can be added to make sure all of the medicine is consumed. Kuvan tablets may also be crushed and then mixed in a small amount of soft foods such as apple sauce or pudding.

Kuvan Powder for Oral Solution

Kuvan powder for oral solution should be dissolved in 120 to 240 mL of water or apple juice and taken orally within 30 minutes of dissolution. Kuvan powder for oral solution may also be stirred in a small amount of soft foods such as apple sauce or pudding. Empty the contents of the packet(s) in water, apple juice, or a small amount of soft foods and mix thoroughly. The powder should dissolve completely.

For infants weighing 10 kg or less, Kuvan can be dissolved in as little as 5 mL of water or apple juice and a portion of this solution corresponding to a 10 mg/kg dose may be administered orally via an oral dosing syringe. Table 1 provides dosing information for infants at the recommended starting dose of 10 mg/kg per day. Refer to Table 2 for dosing information at 20 mg/kg per day if dosage adjustment is needed.

Table 1: 10 mg/kg per day Dosing Table for Infants Weighing 10 kg or less

Patient Weight (kg)	Starting Dose: 10 mg/kg per day*			
	Dose (mg)	# Kuvan 100 mg Packets Dissolved†	Dilution Volume (mL)‡	Administered Dose volume (mL) §
1	10	1	10	1
2	20	1	10	2
3	30	1	10	3
4	40	1	10	4
5	50	1	10	5
6	60	1	5	3
7	70	1	5	3.5
8	80	1	5	4
9	90	1	5	4.5
10	100	1	5	5

*Starting dose for infants is 10 mg/kg per day. Dosing information for 20 mg/kg per day is provided in Table 2.

† Powder for oral solution provided in single use packets containing 100 mg Kuvan per packet

‡ Volume of water or apple juice to dissolve Kuvan Powder for Oral Solution.

§Discard remainder of mixture after volume to be administered is drawn.

Table 2: 20 mg/kg per day Dosing Table for Infants Weighing 10 kg or less

Patient Weight (kg)	20 mg/kg per day			
	Dose (mg)	# Kuvan 100 mg Packets* Dissolved	Dilution Volume (mL)†	Administered Dose volume (mL)§
1	20	1	5	1
2	40	1	5	2
3	60	1	5	3
4	80	1	5	4
5	100	1	5	5
6	120	2	5	3
7	140	2	5	3.5
8	160	2	5	4
9	180	2	5	4.5
10	200	2	5	5

*Powder for oral solution provided in single use packets containing 100 mg Kuvan per packet
† Volume of water or apple juice to dissolve Kuvan Powder for Oral Solution.
§Discard remainder of mixture after volume to be administered is drawn.

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) and as a unit dose packet containing 500 mg of sapropterin dihydrochloride (equivalent to 384 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 Hypophenylalaninemia

In clinical trials, some patients have experienced low blood Phe levels. Children younger than 7 years treated with Kuvan doses of 20 mg/kg per day are at increased risk for low levels of blood Phe compared with patients 7 years and older *[see Adverse Reactions (6.1)]*.

5.4 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)]*.

5.5 Identify Non-Responders to Kuvan Treatment

Not all patients with PKU respond to treatment with Kuvan. In two clinical trials at a dose of 20 mg/kg per day, 56% to 75% of pediatric PKU patients responded to treatment with Kuvan, and in one clinical trial at a dose of 10 mg/kg per day, 20% of adult and pediatric PKU patients responded to treatment with Kuvan *[see Clinical Studies (14.1)]*.

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

5.6 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.

5.7 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.

5.8 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).

5.9 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.

5.10 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.

5.11 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.

<u>PKU Clinical Studies</u>
The safety of Kuvan was evaluated in 6 clinical studies in patients with PKU (aged 1 month to 50 years) *[see Clinical Studies (14.1)]*.

In Studies1-4 (controlled and uncontrolled studies), 579 patients with PKU aged 4 to 49 years received Kuvan in doses ranging from 5 to 20 mg/kg per day for lengths of treatment ranging from 1 to 164 weeks. The patient population was evenly distributed in gender, and approximately 95% of patients were Caucasian. The most common adverse reactions (≥4% of patients) were headache, rhinorrhea, pharyngolaryngeal pain, diarrhea, vomiting, cough, and nasal congestion.

The data described in Table 3 reflect exposure of 74 patients with PKU to Kuvan at doses of 10 to 20 mg/kg per day for 6 to 10 weeks in two double-blind, placebo-controlled clinical trials (Studies 2 and 4).

Table 3 enumerates adverse reactions occurring in at least 4% of patients treated with Kuvan in the double-blind, placebo-controlled clinical trials described above.

Table 3: 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 (Studies 1 and 3) all patients received Kuvan in doses of 5 to 20 mg/kg per 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 Study 5, 65 pediatric patients with PKU aged 1 month to 6 years received Kuvan 20 mg/kg per day for 6 months. Adverse reactions in these patients were similar in frequency and type as those seen in other Kuvan clinical trials except for an increased incidence of low Phe levels. Twenty-five percent (16 out of 65) of patients developed Phe levels below normal for age *[see Warnings and Precautions (5.3), Pediatric Use (8.4), and Clinical Studies (14.1)]*.

In Study 6, a long term, open-label, extension study of 111 patients aged 4 to 50 years, receiving Kuvan in doses ranging from 5 to 20 mg/kg per day, 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. The mean (± SD) exposure to sapropterin for the entire study population was 659 ± 221 days (maximum 953 days).

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 per 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 (5.10)]*, 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, 5.11)]*.

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 per day sapropterin dihydrochloride (about 3 times the MRHD of 20 mg/kg per 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 per 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 Mother

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

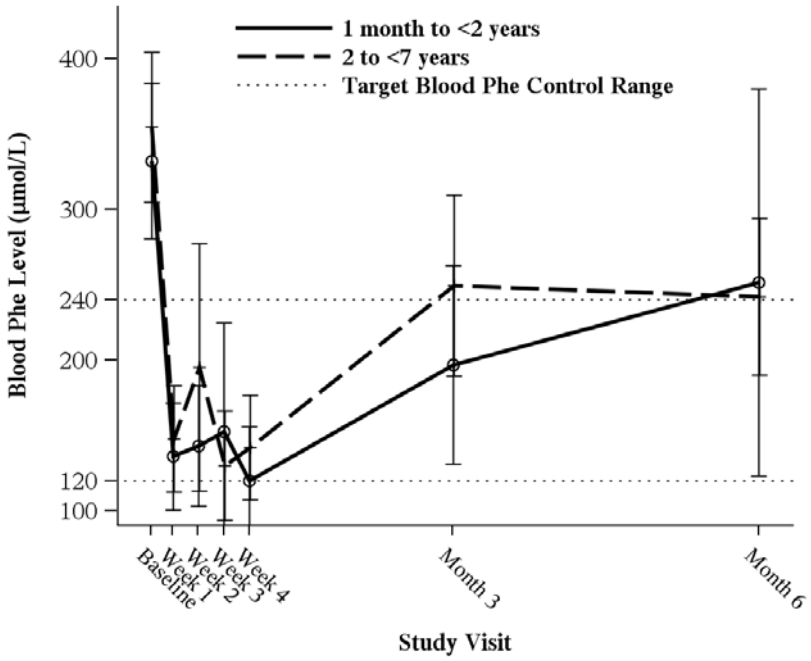
Pediatric patients with PKU, ages 1 month to 16 years, have been treated with Kuvan in clinical trials *[see Clinical Studies (14.1)]*.

The efficacy and safety of Kuvan have not been established in neonates. The safety of Kuvan has been established in children younger than 4 years in trials of 6 months duration and in children 4 years and older in trials of up to 3 years in length *[see Adverse Reactions (6.1)]*.

In children aged 1 month and older, the efficacy of Kuvan has been demonstrated in trials of 6 weeks or less in duration *[see Clinical Studies (14.1)]*.

In a multicenter, open-label, single arm study, 57 patients aged 1 month to 6 years who were defined as Kuvan responders after 4 weeks of Kuvan treatment and Phe dietary restriction were treated for 6 months with Kuvan at 20 mg/kg per day. The effectiveness of Kuvan alone on reduction of blood Phe levels beyond 4 weeks could not be determined due to concurrent changes in dietary Phe intake during the study. Mean (±SD) blood Phe values over time for patients aged 1 month to <2 years and 2 to <7 years are shown in Figure 1.

Figure 1: Mean Blood Phe Level Over Time by Age (years) (N=57)



*Error bars indicate 95% confidence interval.

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 per day instead of 20 mg/kg per day. The patient reported hyperactivity that began at an unspecified time after overdose and resolved after the Kuvan dose was reduced to 20 mg/kg per day.

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

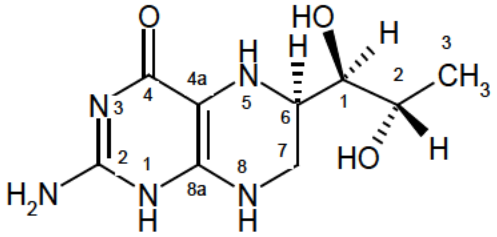
reactions reported in more than 1 subject who received the supra-therapeutic dose were upper abdominal pain (6%) and dizziness (4%). A dose-dependent shortening of the QT interval was observed *[see Clinical Pharmacology (12.2)]*.

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 76.8 mg of sapropterin base). Kuvan is also supplied as powder for oral solution containing 500 mg of sapropterin dihydrochloride (equivalent to 384 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 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 activity, 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 per 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.

Kuvan dose-response relationship was studied in an open-label, forced titration study at doses of 5 mg/kg per day, then 20 mg/kg per day, and then 10 mg/kg per day (Study 3) *[see Clinical Studies (14.1)]*. Individual blood Phe levels were highly variable among patients. The mean blood Phe level observed at the end of each 2-week dosing period decreased as the dose of sapropterin dihydrochloride increased, demonstrating an inverse relationship between the dose of sapropterin dihydrochloride and mean blood Phe levels.

<u>Effects of Kuvan on the QTc interval</u>
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) dose 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}.

Population pharmacokinetic analysis of sapropterin including patients from 1 month to 49 years of age showed that body weight is the only covariate substantially affecting clearance or distribution volume (see Table 4). Pharmacokinetics in patients >49 years of age have not been studied.

Table 4. Apparent Plasma Clearance by Age

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

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

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 per day (0.2, 0.7, and 2 times the maximum recommended human dose of 20 mg/kg per 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 per 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 per 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 per day (about 8 times the maximum recommended human dose of 20 mg/kg per day, based on body surface area). Sapropterin dihydrochloride, at oral doses up to 400 mg/kg per 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 of Kuvan was evaluated in five 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 per 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 per 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 5).

Table 5: Blood Phe Results in Study 2

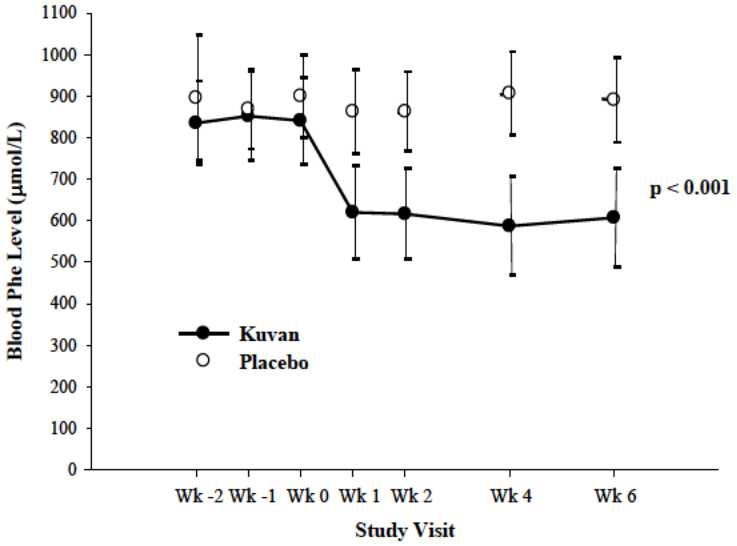
	Sapropterin (N=41)	Placebo (N=47)
Baseline Blood Phe Level* (µmol/L)		
Mean (±SD)	843 (±300)	888 (±323)
Percentiles (25th, 75th)	620, 990	618, 1141
Week 6 Blood Phe Level (µmol/L)		
Mean (±SD)	607 (±377)	891 (±348)
Percentiles (25th, 75th)	307, 812	619, 1143
Mean Change in Blood Phe From Baseline to Week 6 (µmol/L)		
Adjusted Mean (±SE) †	-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

*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.

†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 2).

Figure 2: Mean Blood Phenylalanine (Phe) Level Over Time*



*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 per 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 per day, mean (±SD) blood Phe levels were 744 (±384) μmol/L, 640 (±382) μmol/L, and 581 (±399) μmol/L, respectively (Table 6).

Table 6: Blood Phe Results From Forced Dose-Titration in Study 3

Kuvan Dose Level (mg/kg per 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 pediatric patients 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 per 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 was an open label, single arm, multicenter trial in 93 pediatric patients with PKU, aged 1 month to 6 years, who had Phe levels greater than or equal to 360 μmol/L at screening. All patients were treated with Kuvan at 20 mg/kg per day and maintained on a Phe-restricted diet. At Week 4, 57 patients (61%) were identified as responders (defined as ≥ 30% decreased in blood Phe from baseline) (see Figure 1 section 8.4).

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 68135-300-02 Bottle of 120 tablets

Kuvan powder for oral solution is an off-white to yellow powder packaged in unit dose packets as follows:
100 mg Kuvan per packet:
NDC 68135-301-22 Carton of 30 unit dose packets
NDC 68135-301-11 Single unit dose packet
500 mg Kuvan per packet:
NDC 68135-482-11 Carton of 30 unit dose packets
NDC 68135-482-10 Single unit dose packet

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

Store Kuvan powder for oral solution at 20ºC to 25ºC (68ºF to 77ºF); excursions allowed between 15ºC to 30ºC (59ºF to 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 and Instructions for Use)

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

- Advise patients that Kuvan may cause low blood Phe levels. Advise patients that children younger than 7 years treated with Kuvan doses of 20 mg/kg per day are at increased risk for low levels of blood Phe compared with children 7 years and older. Blood Phe levels that are too low for prolonged periods of time may be associated with catabolism and protein breakdown *[see Warnings and Precautions (5.3)]*.
- Advise patients that Kuvan is to be used in conjunction with a Phe-restricted diet *[see Warnings and Precautions (5.6)]*.
- Advise patients that not all patients with PKU respond to treatment with Kuvan and that response to Kuvan can only be determined by a therapeutic trial *[see Warnings and Precautions (5.4, 5.5)]*.
- Advise patients that they must be evaluated for changes in blood Phe after being treated with Kuvan at the recommended dose(s) for age to determine if they are a responder and that blood Phe levels and dietary Phe intake should be measured frequently during the first month *[see Warnings and Precautions (5.4, 5.5)]*.
- Advise patients that they should have frequent blood Phe measurements and nutritional counseling with their physician and other members of the health care team knowledgeable in the management of PKU to ensure maintenance of blood Phe levels in the desirable range *[see Warnings and Precautions (5.4)]*.
- Advise patients not to 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.
- Advise patients not to continue treatment with Kuvan if they are determined to be a non-responder during the evaluation period *[see Dosage and Administration (2.1)]*.
- Advise patients that reduction of blood Phe levels through dietary control is an important determinant of long-term neurologic outcome in PKU patients. Advise patients that the effect of Kuvan on long-term neurologic function in patients with PKU has not been assessed.
- Advise patients that Kuvan may cause hypersensitivity reactions including anaphylaxis and rash *[see Warnings and Precautions (5.1)]*.

- Advise patients to notify their physician for symptoms of severe gastritis *[see Warnings and Precautions (5.2)]*.
- Advise patients that blood Phe levels that are too high for prolonged periods of time can result in neurologic impairment.
- Advise patients that adequate blood Phe control needs to be maintained to avoid blood Phe levels that are too high or too low.
- Advise patients that to ensure maintenance of adequate blood Phe control, close monitoring is recommended and that the dose of Kuvan should be adjusted if necessary.
- Advise 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, or levodopa that they may require additional clinical monitoring while taking Kuvan*[see Warnings and Precautions (5.7, 5.8, 5.9, 5.10)]*.
- Advise patients that Kuvan may cause hyperactivity *[see Warnings and Precautions (5.11)]*.
- Advise patients that BioMarin has a product registry for PKU patients to 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 doctor 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 a meal. 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. You may also crush the tablets and mix in a small amount of soft food, such as apple sauce or pudding before taking.
  - Be sure that you know what dose of Kuvan powder your doctor prescribed and whether you should use Kuvan 100 mg packets, Kuvan 500 mg packets, or both types of packets to prepare your dose.
  - Open Kuvan powder packets only when you are ready to use them.
  - Kuvan powder for oral solution should be dissolved in water or apple juice. You may also mix the powder for oral solution in a small amount of soft food, such as apple sauce or pudding before taking.
  - See the detailed "Instructions for Use" that comes with Kuvan 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

- **Phe levels that are too low.** Some children under the age of 7 who take high doses of Kuvan each day may experience low Phe levels.

- **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.

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.

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

BIOMARIN

BioMarin Pharmaceutical Inc.

Novato, CA 94949

Revised: 07/2015

© BioMarin Pharmaceutical Inc. All rights reserved.

Kuvan is a registered trademark of BioMarin Pharmaceutical Inc.

v5/2015