

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 adult and pediatric patients one month of age and older 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

All patients with PKU who are being treated with KUVAN should also be treated with a Phe-restricted diet, including dietary protein and Phe restriction. (2.1)

Starting Dosage

- *Pediatric patients 1 month to 6 years:* The recommended starting dosage of KUVAN is 10 mg/kg administered orally once daily. (2.2)
- *Patients 7 years and older:* The recommended starting dosage of KUVAN is 10 to 20 mg/kg administered orally once daily. (2.2)

Dosage Adjustment

- Doses of KUVAN may be adjusted in the range of 5 to 20 mg/kg taken once daily. (2.2)
- Monitor blood Phe regularly, especially in pediatric patients. (2.2, 5.3)

Preparation and Administration

- See the full prescribing information for preparation and administration instructions. (2.3)

DOSAGE FORMS AND STRENGTHS

- Tablets: 100 mg sapropterin dihydrochloride. (3)
- Powder for Oral Solution: 100 mg and 500 mg sapropterin dihydrochloride. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- **Hypersensitivity Reactions Including Anaphylaxis:** KUVAN is not recommended in patients with a history of anaphylaxis to KUVAN; discontinue treatment in patients who experience anaphylaxis and initiate appropriate medical treatment. Continue dietary Phe restrictions. (5.1)
- **Upper Gastrointestinal Mucosal Inflammation:** Monitor patients for signs and symptoms of these conditions including esophagitis and gastritis. (5.2)
- **Hypophenylalaninemia:** Pediatric patients 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. (5.3)
- **Monitoring Blood Phe Levels During Treatment:** Ensure adequate blood Phe control and nutritional balance during treatment with KUVAN. Frequent blood monitoring is recommended, especially in pediatric patients. (5.4, 2.1)
- **Lack of Biochemical Response to KUVAN Treatment:** Response to KUVAN treatment cannot be pre-determined by laboratory (e.g., molecular) testing and can only be determined by a therapeutic trial of KUVAN. (5.5, 2.1)
- **Interaction with Levodopa:** Seizures, over-stimulation or irritability may occur; monitor patients for a change in neurologic status. (5.6, 7)
- **Hyperactivity:** Monitor patients for hyperactivity. (5.7)

ADVERSE REACTIONS

Most common adverse reactions ($\geq 4\%$) are: headache, rhinorrhea, pharyngolaryngeal pain, diarrhea, vomiting, cough, and nasal congestion. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact BioMarin Pharmaceutical Inc. at 1-877-695-8826, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- **Inhibitors of Folate Synthesis (e.g., methotrexate, valproic acid, phenobarbital, trimethoprim):** Can decrease endogenous BH4 levels; monitor blood Phe levels more frequently and adjust KUVAN dosage as needed. (7)
- **Drugs Affecting Nitric Oxide-Mediated Vasorelaxation (e.g., PDE-5 inhibitors):** Potential for vasorelaxation; monitor blood pressure. (7)

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

Revised: 8/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

1	INDICATIONS AND USAGE	6	ADVERSE REACTIONS
2	DOSAGE AND ADMINISTRATION	6.1	Clinical Trials Experience
2.1	Recommendations Prior to KUVAN Treatment	6.2	Postmarketing Experience
2.2	Recommended Dosage and Administration	7	DRUG INTERACTIONS
2.3	Preparation and Administration Instructions	8	USE IN SPECIFIC POPULATIONS
3	DOSAGE FORMS AND STRENGTHS	8.1	Pregnancy
4	CONTRAINDICATIONS	8.2	Lactation
5	WARNINGS AND PRECAUTIONS	8.4	Pediatric Use
5.1	Hypersensitivity Reactions Including Anaphylaxis	8.5	Geriatric Use
5.2	Upper Gastrointestinal Mucosal Inflammation	10	OVERDOSAGE
5.3	Hypophenylalaninemia	11	DESCRIPTION
5.4	Monitoring Blood Phe Levels During Treatment	12	CLINICAL PHARMACOLOGY
5.5	Lack of Biochemical Response to KUVAN	12.1	Mechanism of Action
5.6	Interaction with Levodopa	12.2	Pharmacodynamics
5.7	Hyperactivity	12.3	Pharmacokinetics
		13	NONCLINICAL TOXICOLOGY
		13.1	Carcinogenesis, Mutagenesis, Impairment of Fertility
		14	CLINICAL STUDIES
		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[®] is indicated to reduce blood phenylalanine (Phe) levels in adult and pediatric patients one month of age and older 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 Recommendations Prior to KUVAN Treatment

Treatment with KUVAN should be directed by physicians knowledgeable in the management of PKU.

All patients with PKU who are being treated with KUVAN should also be treated with a Phe-restricted diet, including dietary protein and Phe restriction.

2.2 Recommended Dosage and Administration

The recommended starting dosage of KUVAN is:

Pediatric Patients 1 month to 6 years: 10 mg/kg (actual body weight) administered orally once daily.

Patients 7 years and older: 10 to 20 mg/kg (actual body weight) administered orally once daily.

Administer KUVAN with a meal, preferably at the same time each day [*see Clinical Pharmacology (12.3)*].

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

Evaluation Period

Existing dietary protein and Phe intake should not be modified during the evaluation period.

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 do not show a biochemical response 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 show a biochemical response (blood Phe does not decrease) after 1 month of treatment at 20 mg/kg per day [*see Warnings and Precautions (5.4)*].

Dosage Adjustment

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 biochemical response to therapy (blood Phe). Periodic blood Phe monitoring is recommended to assess blood Phe control, especially in pediatric patients [*see Warnings and Precautions (5.3)*].

2.3 Preparation and Administration Instructions

KUVAN Tablets

- 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

Patients weighing greater than 10 kg

- 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 food 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.

Patients weighing 10 kg or less (use 100 mg packets)

- For infants weighing 10 kg or less, KUVAN powder for oral solution 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 Powder for Oral Solution 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 Powder for Oral Solution 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 soproterin dihydrochloride. 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 soproterin dihydrochloride and as a unit dose packet containing 500 mg of soproterin dihydrochloride. 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 protein and Phe restriction in patients who experience anaphylaxis.

5.2 Upper Gastrointestinal Mucosal Inflammation

Gastrointestinal (GI) adverse reactions suggestive of upper GI mucosal inflammation have been reported with KUVAN. Serious adverse reactions included esophagitis and gastritis [*see Adverse Reactions (6.2)*]. If left untreated, these could lead to severe sequelae including esophageal stricture, esophageal ulcer, gastric ulcer, and bleeding and such complications have been reported in patients receiving KUVAN. Monitor patients for signs and symptoms of upper GI mucosal inflammation.

5.3 Hypophenylalaninemia

In clinical trials of KUVAN, some PKU patients experienced hypophenylalaninemia (low blood Phe) during treatment with KUVAN. In a clinical study of pediatric patients younger than 7 years old treated with KUVAN 20 mg/kg per day, the incidence of hypophenylalaninemia was higher than in clinical trials of older patients [*see Adverse Reactions (6.1)*].

5.4 Monitoring Blood Phe Levels During Treatment

Prolonged elevations of blood Phe levels in patients with PKU can result in severe neurologic damage, including severe intellectual disability, developmental delay, microcephaly, delayed speech, seizures, and behavioral abnormalities. Conversely, prolonged levels of blood Phe that are too low have been associated with catabolism and endogenous protein breakdown, which has been associated with adverse developmental outcomes. 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 Dosage and Administration (2.2)*].

5.5 Lack of Biochemical Response to KUVAN

Some patients with PKU do not show biochemical response (reduction in blood Phe) with treatment with KUVAN. In two clinical trials at a KUVAN dose of 20 mg/kg per day, 56% to 75% of pediatric PKU patients showed a biochemical response to KUVAN, and in one clinical trial at a dose of 10 mg/kg per day, 20% of adult and pediatric PKU patients showed a biochemical response to KUVAN [*see Clinical Studies (14)*].

Biochemical response to KUVAN treatment cannot generally be pre-determined by laboratory testing (e.g., molecular testing), and should be determined through a therapeutic trial (evaluation) of KUVAN response [*see Dosage and Administration (2.2)*].

5.6 Interaction with Levodopa

In a 10-year post-marketing safety surveillance program for a non-PKU indication using another sapropterin product, 3 patients with underlying neurological disorders experienced seizures, exacerbation of seizures, over-stimulation, and irritability during co-administration of levodopa and sapropterin. Monitor patients who are receiving levodopa for changes in neurological status during treatment with KUVAN [*see Drug Interactions (7)*].

5.7 Hyperactivity

In the KUVAN postmarketing safety surveillance program, 2 patients with PKU experienced hyperactivity when treated with KUVAN [see Adverse Reactions (6.2)]. Monitor patients for hyperactivity.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction 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

The safety of KUVAN was evaluated in 7 clinical studies in patients with PKU (aged 1 month to 50 years) [see Clinical Studies (14)].

In Studies 1-4 (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 ($\geq 4\%$ 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 $\geq 4\%$ 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, and adverse reactions were similar in type and frequency to those reported in the double-blind, placebo-controlled clinical trials [see *Clinical Studies (14)*].

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)*, *Use In Specific Populations (8.4)*, and *Clinical Studies (14)*].

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 (\pm SD) exposure to sapropterin for the entire study population was 659 ± 221 days (maximum 953 days).

In Study 7, 27 pediatric patients with PKU aged 0 to 4 years received KUVAN 10 mg/kg per day or 20 mg/kg per day. Adverse reactions were similar in type and frequency to those observed in other clinical trials, with the addition of rhinitis, which was reported in 2 subjects (7.4%).

Safety Experience from Clinical Studies for Non-PKU Indications

Approximately 800 healthy subjects 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 seizures, exacerbation of seizures [see *Warnings and Precautions (5.3)*], 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 Postmarketing Experience

The following adverse reactions have been reported 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 a causal relationship to drug exposure.

Hypersensitivity reactions including anaphylaxis and rash: Most hypersensitivity reactions occurred within several days of initiating treatment [see *Warnings and Precautions (5.1)*].

Gastrointestinal reactions: esophagitis, gastritis, oropharyngeal pain, pharyngitis, esophageal pain, abdominal pain, dyspepsia, nausea, and vomiting [see *Warnings and Precautions (5.2)*].

Hyperactivity: Two cases have been reported. In one case, the patient received an accidental overdose of KUVAN [see *Warnings and Precautions (5.6), Overdosage (10)*].

7 DRUG INTERACTIONS

Table 4 includes drugs with clinically important drug interactions when administered with sapropterin dihydrochloride and instructions for preventing or managing them.

Table 4: Clinically Relevant Drug Interactions

Levodopa	
<i>Clinical Impact</i>	Sapropterin dihydrochloride may increase the availability of tyrosine, a precursor of levodopa. Neurologic events were reported postmarketing in patients receiving sapropterin and levodopa concomitantly for a non-PKU indication [see <i>Warnings and Precautions (5.5)</i>].
<i>Intervention</i>	Monitor patients for a change in neurologic status.
Inhibitors of Folate Synthesis (e.g., methotrexate, valproic acid, phenobarbital, trimethoprim)	
<i>Clinical Impact</i>	In vitro and in vivo nonclinical data suggest that drugs that inhibit folate synthesis may decrease the bioavailability of endogenous BH4 by inhibiting the enzyme dihydrofolate reductase, which is involved in the recycling (regeneration) of BH4. This reduction in net BH4 levels may increase Phe levels.
<i>Intervention</i>	Consider monitoring blood Phe levels more frequently during concomitant administration. An increased dosage of KUVAN may be necessary to achieve a biochemical response.
Drugs Affecting Nitric Oxide-Mediated Vasorelaxation (e.g., PDE-5 inhibitors such as sildenafil, vardenafil, or tadalafil)	
<i>Clinical Impact</i>	Both sapropterin dihydrochloride and PDE-5 inhibitors may induce vasorelaxation. A reduction in blood pressure could occur; however, the combined use of these medications has not been evaluated in humans.
<i>Intervention</i>	Monitor blood pressure.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from pregnancy safety studies, pharmacovigilance, and published case reports with KUVAN use during pregnancy have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes (*see Data*). Uncontrolled blood phenylalanine concentrations before and during pregnancy are associated with an increased risk of adverse pregnancy outcomes and fetal adverse effects (*see Clinical Considerations*).

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.

All pregnancies have a background risk of major birth defects, pregnancy loss, or other adverse pregnancy outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. The estimated background risk of major birth defects and miscarriage in pregnant women with PKU who maintain blood phenylalanine concentrations greater than 600 micromol/L during pregnancy is greater than the corresponding background risk for pregnant women without PKU.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-Fetal Risk

Uncontrolled blood phenylalanine concentrations before and during pregnancy are associated with an increased risk of adverse pregnancy outcomes and fetal adverse effects. To reduce the risk of hyperphenylalaninemia-induced fetal adverse effects, blood phenylalanine concentrations should be maintained between 120 and 360 micromol/L during pregnancy and during the 3 months before conception [*see Dosage and Administration 2.2*].

Data

Human Data

Uncontrolled Maternal PKU

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 micromol/L are associated with a very high incidence of neurological, cardiac, facial dysmorphism, and growth anomalies. Control of blood phenylalanine during pregnancy is essential to reduce the incidence of Phe-induced teratogenic effects.

Pregnancy Registry Data

Available data from pregnancy sub-registries within the Phenylketonuria Developmental Outcomes and Safety (PKUDOS) Registry and the KUVAN Adult Maternal Pediatric European Registry (KAMPER) have identified 72 live births (79 pregnancies) in women with PKU exposed to sapropterin during pregnancy. Three birth defects were reported, including one case each of microcephaly, cleft palate, and tongue tie. The two major birth defects (microcephaly and cleft palate) were associated with Phe levels greater than 360 micromol/L during pregnancy.

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).

8.2 Lactation

Risk Summary

There are insufficient data to assess the presence of sapropterin in human milk and no data on the effects on milk production. In postmarketing pregnancy registries, 13 infants were exposed to KUVAN through breastfeeding. No lactation-related safety concerns were reported in infants of mothers nursing during maternal treatment with KUVAN. There are no data on the effects on milk production. Sapropterin is present in the milk of lactating rats following intravenous administration, but not following oral administration.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for KUVAN and any potential adverse effects on the breastfed child from KUVAN or from the underlying maternal condition.

8.4 Pediatric Use

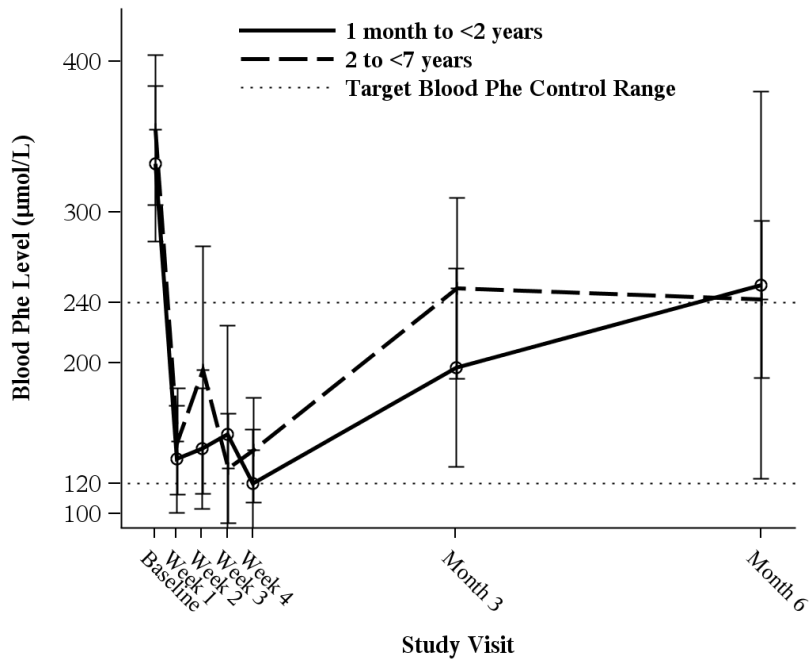
Pediatric patients with PKU, ages 1 month to 16 years, have been treated with KUVAN in clinical trials [*see Clinical Studies (14)*].

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)*].

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 (\pm 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.

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 overdosage 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)].

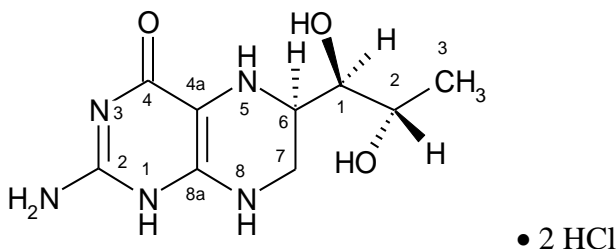
Patients should be advised to notify their physicians in cases of overdosage.

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 C₉H₁₅N₅O₃·2HCl with a molecular weight of 314.17.

Sapropterin dihydrochloride has the following structural formula:



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.

Cardiac Electrophysiology

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 subjects 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 hours), comparable with values seen in healthy subjects (range 3.0 to 5.3 hours).

A study in healthy adults with 10 mg/kg of KUVAN demonstrated that 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} [*see Dosage and Administration (2.3)*].

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 5). Pharmacokinetics in patients >49 years of age have not been studied.

Table 5: 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.

Drug Interaction Studies

Clinical Studies

In healthy subjects, administration of a single dose of KUVAN at the maximum therapeutic dose of 20 mg/kg had no effect on the pharmacokinetics of a single dose of digoxin (P-gp substrate) administered concomitantly.

In Vitro Studies Where Drug Interaction Potential Was Not Further Evaluated Clinically

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

In vitro sapropterin did not inhibit OAT1, OAT3, OCT2, MATE1, and MATE2-K transporters. The potential for sapropterin to inhibit OATP1B1 and OATP1B3 has not been adequately studied. In vitro, sapropterin inhibits breast cancer resistance protein (BCRP) but the potential for a clinically significant increase in systemic exposure of BCRP substrates by KUVAN appears to be low.

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

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 $\geq 30\%$ 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 (\pm SD) blood Phe level was 843 (\pm 300) µmol/L in the KUVAN-treated group and 888 (\pm 323) µmol/L in the placebo group. At Week 6, the KUVAN treated group had a mean (\pm SD) blood Phe level of 607 (\pm 377) µmol/L, and the placebo group had a mean blood Phe level of 891 (\pm 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% (\pm 32) and 3% (\pm 33), respectively). The difference between the groups was statistically significant ($p < 0.001$) (Table 6).

Table 6: Blood Phe Results in Study 2

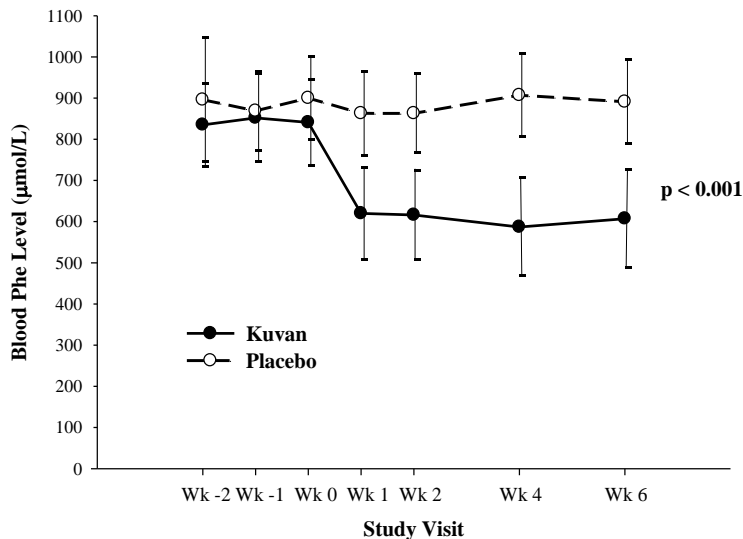
	Sapropterin (N=41)	Placebo (N=47)
Baseline Blood Phe Level* ($\mu\text{mol/L}$)		
Mean ($\pm\text{SD}$)	843 (± 300)	888 (± 323)
Percentiles (25 th , 75 th)	620, 990	618, 1141
Week 6 Blood Phe Level ($\mu\text{mol/L}$)		
Mean ($\pm\text{SD}$)	607 (± 377)	891 (± 348)
Percentiles (25 th , 75 th)	307, 812	619, 1143
Mean Change in Blood Phe From Baseline to Week 6 ($\mu\text{mol/L}$)		
Adjusted Mean ($\pm\text{SE}$) †	-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 ($\pm\text{SD}$)	- 29 (± 32)	3 (± 33)
Percentiles (25 th , 75 th)	-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 (\pm SD) blood Phe was 844 (\pm 398) μ mol/L. At the end of treatment with 5, 10, and 20 mg/kg per day, mean (\pm SD) blood Phe levels were 744 (\pm 384) μ mol/L, 640 (\pm 382) μ mol/L, and 581 (\pm 399) μ mol/L, respectively (Table 7).

Table 7: Blood Phe Results From Forced Dose-Titration in Study 3

KUVAN Dose Level (mg/kg per day)	No. of Patients	Mean (\pmSD) Blood Phe Level (μmol/L)	Mean Changes (\pmSD) in Blood Phe Level From Week 0 (μmol/L)
Baseline (No Treatment)	80	844 (\pm 398)	—
5	80	744 (\pm 384)	-100 (\pm 295)
10	80	640 (\pm 382)	-204 (\pm 303)
20	80	581 (\pm 399)	-263 (\pm 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 \leq 480 μ mol/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 \geq 30% decrease in blood Phe from baseline at Day 8. At Day 8, 50 patients (56%) had a \geq 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 μ mol/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 \geq 30% decreased in blood Phe from baseline) [see Use in Specific Populations (8.4) Figure 1].

16 HOW SUPPLIED/STORAGE AND HANDLING

KUVAN Tablets

100 mg sapropterin dihydrochloride, 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 for Oral Solution

Supplied as an off-white to yellow powder supplied in unit dose packets as follows:

100 mg sapropterin dihydrochloride per packet:

NDC 68135-301-22 Carton of 30 unit dose packets

NDC 68135-301-11 Single unit dose packet

500 mg sapropterin dihydrochloride 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 20°C to 25°C (68°F to 77°F); excursions allowed between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Keep container tightly closed. Protect from moisture.

Store KUVAN for oral solution at 20°C to 25°C (68°F to 77°F); excursions allowed between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture.

17 PATIENT COUNSELING INFORMATION

Advise the patient or caregiver to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Hypersensitivity Reactions Including Anaphylaxis

Advise patients and caregivers to discontinue KUVAN and contact the patient's healthcare provider immediately if they experience symptoms of anaphylaxis, including (but not limited to) wheezing, dyspnea, coughing, hypotension, flushing, nausea, and rash. Continue nutritional management including dietary protein and Phe restriction [see *Warnings and Precautions (5.1)*].

Upper Gastrointestinal Mucosal Inflammation

Advise patients and caregivers to contact their healthcare provider if the patient experiences signs and symptoms suggestive of upper GI mucosal inflammation, including nausea, vomiting, dysphagia, dyspepsia, loss of appetite; oropharyngeal, esophageal, or upper abdominal pain [see *Warnings and Precautions (5.3)*].

Hypophenylalaninemia

Advise patients and caregivers that KUVAN may cause hypophenylalaninemia (low blood Phe levels), especially in pediatric patients younger than 7 years of age [see *Warnings and Precautions (5.3)*].

Monitoring of Blood Phe Levels

Advise patients and caregivers that frequent blood Phe monitoring is important to ensure blood Phe levels are in the desirable range and that they should maintain dietary protein and Phe restriction while on KUVAN [see *Warnings and Precautions (5.4)*].

Prolonged hyperphenylalaninemia (high blood Phe levels) in patients with PKU can result in severe neurologic damage, including intellectual disability, developmental delay, microcephaly, delayed speech, seizures, and behavioral abnormalities [see *Warnings and Precautions (5.4)*].

Lack of Biochemical Response to KUVAN

Some patients do not show a biochemical response (blood Phe reduction) when treated with KUVAN. Advise patients and caregivers to discontinue treatment with KUVAN if the patient does not show an adequate biochemical response in blood Phe after one month of treatment with KUVAN 20 mg/kg per day [see *Dosage and Administration (2.2)*, *Warnings and Precautions (5.4)*].

Interaction with Levodopa

Advise patients and caregivers that patients with underlying neurological disorders taking KUVAN in combination with levodopa may experience seizures, exacerbation of seizures, over-stimulation or irritability. Inform patients and caregivers to contact their healthcare provider if the patient has a change in neurologic status during treatment with KUVAN [*see Warnings and Precautions (5.5)*].

Hyperactivity

Advise patients and caregivers that KUVAN may cause hyperactivity and to contact their healthcare provider if the patient experiences hyperactivity, restlessness, fidgeting, or excessive talking [*see Warnings and Precautions (5.6)*].

Dosing and Monitoring [*see Dosage and Administration (2.2)*]

Advise patients and caregivers of the following:

- KUVAN should be used in conjunction with a PKU-specific diet, including dietary protein and Phe restriction.
- Dietary protein and Phe intake should not be modified during the KUVAN evaluation period when assessing biochemical response.
- The patient must be evaluated for changes in blood Phe after being treated with KUVAN at the recommended dose(s) for age to determine if they have a biochemical response and that blood Phe levels and dietary Phe intake should be assessed frequently during the first month of KUVAN treatment.
- Monitoring of blood Phe levels is important during KUVAN treatment.

Preparation and Administration [*see Dosage and Administration (2.3)*]

Advise patients and caregivers:

- KUVAN tablets can be swallowed whole, dissolved in water or apple juice, or crushed and mixed with a small amount of soft food such as apple sauce or pudding.
- KUVAN powder for oral solution should be dissolved in water or apple juice or stirred in a small amount of soft food such as apple sauce or pudding.
- Take KUVAN with a meal, preferably at the same time each day.

Manufactured for:

BioMarin Pharmaceutical Inc.

Novato, CA 94949