KUVAN®
(sapropterin dihydrochloride) Tablets

Extra help for people with PKU

Find out if KUVAN is right for you

KUVAN® (sapropterin dihydrochloride) Tablets are **approved to reduce blood Phe levels in** patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin- **(BH4-) responsive Phenylketonuria (PKU)**. KUVAN is to be used in conjunction with a low-Phe diet.

Take advantage of a

FREE 30-Day Starter of KUVAN

to find out if it's your key to lower Phe!

Please note the free starter supply of KUVAN is only available in the United States and in clinics that have enrolled to participate; not all US clinics are participating at this time. BioMarin reserves the right to change or discontinue this program at any time.

STEP 1 Sign up for the **FREE** 30-Day Starter at KUVAN.com
Expect a call from a KUVAN representative

STEP 2 Make a clinic appointment
to obtain a prescription from your doctor

STEP 3 Start **KUVAN**

For more information about **KUVAN** and to sign up for a **Free 30-Day Starter**, please call or visit our web site at:

www.KUVAN.com
1-877-MY-KUVAN
(1-877-695-8826)

IMPORTANT SAFETY INFORMATION

High blood Phe levels are toxic to the brain and can lead to lower intelligence and decrease in the ability to focus, remember and organize information. Any change you make to your diet may impact your blood Phe level. Follow your doctor's instructions carefully. Your doctor and dietitian will continue to monitor and may adjust your diet throughout your treatment with KUVAN.

If you have a fever, or if you are sick, your Phe level may go up. Tell your doctor and dietitian as soon as possible so they can see if they have to adjust your treatment to help keep your blood Phe levels in the desired range.

KUVAN is a prescription medicine and should not be taken by people who are allergic to any of its ingredients. Tell your doctor if you have ever had liver or kidney problems, are nursing or pregnant or may become pregnant, have poor nutrition or are anorexic. Your doctor will decide if KUVAN is right for you. Tell your doctor about all the medicines you take.

The most common side effects reported when using KUVAN are headache, diarrhea, abdominal pain, upper respiratory tract infection (like a cold), throat pain, vomiting, and nausea.

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.

Please see full prescribing information on the next page.

KUVAN®
(saproterin dihydrochloride) Tablets

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 (saproterin dihydrochloride) Tablets

Initial U.S. Approval: 2007

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

Kuvan 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 (1).

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

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

Doses of Kuvan may be adjusted in the range of 5 to 20 mg/kg taken once daily. Blood Phe must be monitored regularly (2.1).

Kuvan should be taken orally with food to increase the absorption. Kuvan Tablets should be dissolved in 4 to 8 oz. (120-240 mL) of water or apple juice and taken within 15 minutes (2.2).

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

100 mg tablets (3).

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

None (4).

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

Monitor Blood Phe Levels During Treatment:

Prolonged exposure to elevated blood Phe levels can injure the brain and reduce brain function. To ensure adequate blood Phe control, blood Phe levels must still be carefully monitored even though patients are receiving Kuvan which can reduce blood Phe levels (5.1).

Treat All Patients With a Phe-restricted Diet:

The initiation of Kuvan therapy does not eliminate the need for ongoing dietary management (5.3).

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

The most common adverse reactions (incidence ≥4%) in patients treated with Kuvan are headache, diarrhea, abdominal pain, upper respiratory tract infection, pharyngolaryngeal pain, vomiting, and nausea (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*.

---------- USE IN SPECIFIC POPULATIONS----------

Pregnancy Category C. This drug should be used during pregnancy only if clearly needed. There are no adequate and well-controlled studies in pregnant women. Women who are exposed to Kuvan during pregnancy are encouraged to enroll in the Kuvan patient registry (8.1, 17.5).

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

Revision Date: 12/2007

FULL PRESCRIBING INFORMATION: CONTENTS*

*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 patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin- (BH4-) responsive Phenylketonuria (PKU). Kuvan is to be used in conjunction with a Phe-restricted diet.

2. DOSAGE AND ADMINISTRATION

2.1 Dosage

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

Response to therapy is determined by change in blood Phe following treatment with Kuvan at 10 mg/kg/day for a period of up to 1 month. Blood Phe levels should be checked after 1 week of Kuvan treatment and periodically for up to a month. If blood Phe does not decrease from baseline at 10 mg/kg/day, the dose may be increased to 20 mg/kg/day. Patients whose blood Phe does not decrease after 1 month of treatment at 20 mg/kg/day are non-responders, and treatment with Kuvan should be discontinued in these patients.

Once responsiveness to Kuvan has been established, the dosage may be adjusted within the range of 5 to 20 mg/kg/day according to response to therapy. Doses of Kuvan above 20 mg/kg/day have not been evaluated in clinical trials.

2.2 Administration

Kuvan (saproterin dihydrochloride) Tablets should be administered orally with food to increase absorption, preferably at the same time each day. Kuvan Tablets should be dissolved in 4 to 8 oz. (120 to 240 mL) of water or apple juice and taken within 15 minutes of dissolution. It may take a few minutes for the tablets to dissolve. To make the tablets dissolve faster, stir or crush them. The tablets may not dissolve completely. Patients may see small pieces floating on top of the water or apple juice. This is normal and safe for patients to swallow. If after drinking the medicine patients still see pieces of the tablet, they can add more water or apple juice to make sure that they take all of the medicine. A missed dose should be taken as soon as possible, but 2 doses should not be taken on the same day.

3. DOSAGE FORMS AND STRENGTHS

Kuvan (saproterin dihydrochloride) Tablets are unscored, uncoated, immediate-release tablets for oral use. Each tablet contains 100 mg of saproterin dihydrochloride (equivalent to 76.8 mg of saproterin base). Tablets are round, off-white to light yellow, mottled, and debossed with "177".

4. CONTRAINDICATIONS

None.

5. WARNINGS AND PRECAUTIONS

5.1 Monitor Blood Phe Levels During Treatment

Treatment with Kuvan should be directed by physicians knowledgeable in the management of PKU. Prolonged elevations in blood Phe levels in patients with PKU can result in severe neurologic damage, including severe mental retardation, microcephaly, delayed speech, seizures, and behavioral abnormalities. This may occur even if patients are taking Kuvan but not adequately controlling their blood Phe levels within recommended target range. Long-term studies of neurocognitive outcomes with Kuvan treatment have not been conducted. 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.

5.2 Identify Non-Responders to Kuvan Treatment

Not all patients with PKU respond to treatment with Kuvan. In clinical trials, approximately 20% to 56% of PKU patients responded to treatment with Kuvan [see *Clinical Studies (14.1)*]. Response to treatment cannot be pre-determined by laboratory testing (e.g., genetic testing), and can only be determined by a therapeutic trial of Kuvan [see *Dosage and Administration (2.1)*].

5.3 Treat All Patients With a Phe-restricted Diet

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

5.4 Use With Caution in Patients With Hepatic Impairment

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

5.5 Monitor for Allergic Reactions

Patients who have a known severe allergy to any of the components of Kuvan should not take Kuvan. In clinical trials conducted with Kuvan, no severe allergic reactions were observed. The risks and benefits of continued treatment with Kuvan in patients with mild to moderate allergic reactions (such as rash) should be considered.

5.6 Use With Caution When Co-administering Kuvan and Medications Known to Inhibit Folate Metabolism

Drugs known to affect folate metabolism (e.g., methotrexate) and their derivatives should be used with caution while taking Kuvan because these drugs can decrease BH4 levels by inhibiting the enzyme dihydropteridine reductase (DHPR).

5.7 Use With Caution When Co-administering Kuvan and Drugs Known to Affect Nitric Oxide-Mediated Vasorelaxation

Caution should be used with the administration of Kuvan to patients who are receiving drugs that affect nitric oxide-mediated vasorelaxation (e.g., PDE-5 inhibitors such as sildenafil, vardenafil, or tadalafil), because both saproterin dihydrochloride and PDE-5 inhibitors may induce vasorelaxation. The additive effect of saproterin 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.

5.8 Use With Caution When Co-administering Kuvan and Levodopa

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

6. ADVERSE REACTIONS

6.1 Clinical Trials Experience in PKU

In clinical trials, Kuvan has been administered to 579 patients with PKU in doses ranging from 5 to 20 mg/kg/day for lengths of treatment ranging from 1 to 30 weeks. Patients were aged 4 to 49 years old. The patient population was nearly evenly distributed in gender, and approximately 95% of patients were Caucasian.

The most serious adverse reactions during Kuvan administration (regardless of relationship to treatment) were gastritis, spinal cord injury, streptococcal infection, testicular carcinoma, and urinary tract infection. Mild to moderate neutropenia was noted during Kuvan administration in 24 of 579 patients (4%). The most common (≥4% of patients treated with Kuvan) across all studies (n=579) were headache, diarrhea, abdominal pain, upper respiratory tract infection, pharyngolaryngeal pain, vomiting, and nausea.

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

Because clinical trials were conducted under varying conditions, the observed adverse reaction rates may not predict the rates observed in patients in clinical practice. Table 1 enumerates treatment-emergent adverse reactions (regardless of relationship) that occurred in at least 4% of patients treated with Kuvan in the double-blind, placebo-controlled clinical trials described above. Reported frequency of adverse reactions was classified by MedDRA terms (Table 1).

Table 1: Summary of Adverse Reactions by Preferred Term Occurring in ≥4% of Patients in Controlled Clinical Studies With Kuvan

	Treatment	
	Kuvan	**Placebo**
Patients Treated	N = 74	N = 59
Preferred Term	N (%)	N (%)
Any Adverse Reaction	47 (64)	42 (71)
Headache	11 (15)	8 (14)
Upper respiratory tract infection	9 (12)	14 (24)
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)
Pyrexia	5 (7)	4 (7)
Contusion	4 (5)	1 (2)
Abdominal pain	4 (5)	5 (8)
Rash	4 (5)	4 (7)
Nasal congestion	3 (4)	0

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

6.2 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 (saproterin) in approximately 19 controlled and uncontrolled clinical trials. In these clinical trials, subjects were administered saproterin at doses ranging from 1 to 20 mg/kg/day for lengths of exposure from 1 day to 2 years. Serious and severe adverse reactions (regardless of relationship) during saproterin administration were convulsions, exacerbation of convulsions [see *Warnings and Precautions (5.8)*], 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, and upper respiratory tract infection.

6.3 Post-Marketing Experience

The following adverse reactions have been identified during a 10-year post-approval safety surveillance program in Japan of another formulation of the same active ingredient (saproterin). This safety surveillance program was conducted in 30 patients, 27 of whom had disorders other than PKU and had an underlying neurologic condition. The most common adverse reactions were convulsions and exacerbation of convulsions in 3 of the non-PKU patients [see *Warnings and Precautions (5.8)*], and increased gamma-glutamyltransferase (GGT) in 2 of the non-PKU patients.

7. DRUG INTERACTIONS

No drug interaction studies were performed.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Women who are exposed to Kuvan during pregnancy are encouraged to enroll in the Kuvan patient registry [see *Patient Counseling Information (17.5)*].

Teratogenicity studies with saproterin have been conducted in rats at oral doses up to 400 mg/kg/day (about 3 times the maximum recommended human dose of 20 mg/kg/day, based on body surface area) and in rabbits at oral doses of up to 600 mg/kg/day (about 10 times the maximum recommended human dose, based on body surface area). No clear evidence of teratogenic activity was found in either species; however, in the rabbit teratogenicity study, there was an increase (not statistically significant) in the incidence of holoprosencephaly at the 600 mg/kg/day dose compared to controls.

There are no adequate and well-controlled studies of Kuvan in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. A study of 468 pregnancies and 331 live births in PKU-affected women (Maternal Phenylketonuria Collaborative Study, Rouse 1997) has 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 in reducing the incidence of Phe-induced teratogenic effects.

8.2 Labor and Delivery

The effects of Kuvan on labor and delivery in pregnant women are unknown.

8.3 Nursing Mothers

Saproterin is excreted in the milk of intravenously, but not orally treated lactating rats. It is not known whether saproterin is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from saproterin and because of the potential for tumorigenicity shown for saproterin in the rat carcinogenicity study, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Pediatric patients with PKU, ages 4 to 16 years, have been treated with Kuvan in clinical studies [see *Clinical Studies (14.1)*]. The safety and efficacy of Kuvan in pediatric patients less than 4 years of age have not been assessed in clinical studies.

17.6 FDA-Approved Patient Information Labeling

PHARMACIST— DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

PATIENT INFORMATION

For people with PKU

Kuvan (COO-van)
(saproterin dihydrochloride) Tablets

Read this leaflet before you start taking Kuvan and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or treatment.

What is Kuvan?

Kuvan is a medicine for people with Phenylketonuria (PKU). An enzyme in your body PAH (phenylalanine hydroxylase) helps break down phenylalanine (Phe), an amino acid found in food. In patients with PKU this enzyme does not work right. PKU leads to high blood Phe levels. High blood Phe levels are toxic to the brain and can lead to lower intelligence and decrease in the ability to focus, remember, and organize information.

How does Kuvan work?

Kuvan acts in your body with the enzyme PAH to reduce your blood Phe levels. Your doctor and health care team will continue to monitor your blood Phe levels and dietary Phe intake.

Kuvan are tablets that you should dissolve in water or apple juice before taking.

Who may benefit from taking Kuvan?

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

What are the risks of taking Kuvan?

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

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 see if they have to adjust your treatment to help keep your blood Phe levels in the desired range.

What should I tell my doctor before taking Kuvan?

Before you start taking Kuvan, let your doctor know about all of your medical conditions, including if you:

- Have a fever
- Are pregnant or planning to become pregnant
- Are breast feeding
- Have liver problems
- Are allergic to Kuvan or any other medications
- Have poor nutrition or are anorexic
- Are taking levodopa
- Are taking drugs that inhibit folate metabolism (e.g., methotrexate) because these drugs could affect how Kuvan works in your body
- Are taking medicines for erectile dysfunction like Viagra (sildenafil), Levitra (vardenafil), or Cialis (tadalafil)

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

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

How should I take Kuvan?

Kuvan Tablets are taken at one time each day. Take Kuvan exactly as your doctor has told you.

- Take Kuvan once a day with food and preferably at the same time each day.
- Kuvan Tablets should be dissolved in 4 to 8 ounces (1/2 to 1 cup) of water or apple juice.
- To dissolve the tablets, mix them in water or apple juice, and drink within 15 minutes.
  - It may take a few minutes for the tablets to dissolve. To make the tablets dissolve faster, you can stir or crush them.
  - The tablets may not dissolve completely. You may see small pieces floating on top of the water or apple juice. This is normal and safe for you to swallow.
  - If after drinking your medicine you still see small pieces of the tablet, you should add more water or apple juice to make sure that you take all of your medicine.