

PKU, KUVAN, and Your Child

Making smart choices for PKU treatment



An educational brochure brought to you by BioMarin Pharmaceutical Inc.

KUVAN[®]
(sapropterin dihydrochloride) Tablets



Low-Phe diet

+

KUVAN[®]

(sapropterin dihydrochloride) Tablets

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Indication

KUVAN[®] (sapropterin dihydrochloride) Tablets is a prescription medication approved to reduce blood Phe levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin (BH4)-responsive phenylketonuria (PKU). KUVAN is to be used with a Phe-restricted diet.

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 and remember, and organize information. Any change you make to your diet may affect 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 the enclosed KUVAN patient package insert for more information.

KUVAN—Extra help for living with PKU

The more you know about **PKU**, the better you can help your child manage it. The same is true about medicine for PKU.

On the next pages you will learn more about KUVAN (**sapropterin dihydrochloride**) Tablets. In clinical trials, KUVAN was proven to safely help reduce the level of **Phe** in many people with PKU.

Is KUVAN right for your child?

Learn the facts about KUVAN. Then talk to your doctor. Together, you and your doctor can decide if KUVAN is a good choice to help you manage your child's PKU.

Words in **GREEN** are defined on the back page of this booklet.

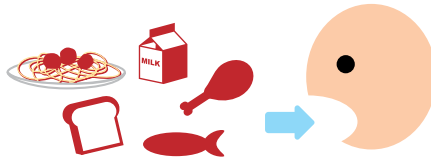
"As the first drug for the treatment of PKU, KUVAN has the potential to revolutionize therapy for patients who are responsive to it, by helping them achieve improved metabolic control. The fact that KUVAN is administered once daily is also a major advantage."

Barbara K. Burton, MD
Professor of Pediatrics
Northwestern University
Medical School

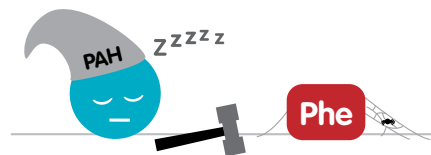


PKU: the Problem

1 Foods with Phe are eaten



2 A defective enzyme (PAH) in the body fails to break down the Phe



3 This leads to high Phe levels in the blood



4 This leads to problems in thinking and behavior



PKU: the Answer

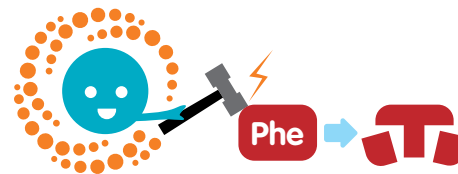
1 Follow a Phe-restricted diet



2 Take KUVAN once daily



3 This stimulates PAH enzyme activity



4 Together, diet and KUVAN lower Phe levels



KUVAN works WITH your child's diet for better control

KUVAN, used along with diet, can help some children with PKU reduce Phe levels in their blood more than the use of diet alone.

How KUVAN works

PKU is caused by a defect in an enzyme called PAH. In a healthy person, the PAH enzyme uses BH4, a chemical naturally present in the body, to break down Phe into other chemicals that help with brain function.

In PKU, the PAH enzyme doesn't break down Phe. Too much Phe builds up in the blood. High levels of Phe affect the brain if left untreated.

KUVAN provides the body with a pharmaceutical form of BH4. This helps the PAH enzyme "wake up" and start breaking down Phe. This helps keep Phe levels in the blood low.

Words in GREEN are defined on the last page of this booklet.

"I chose KUVAN for my daughter because we have always been careful to keep Shayna's Phe levels in a safe range. KUVAN helps us feel that we're doing all we can to keep her levels lower."

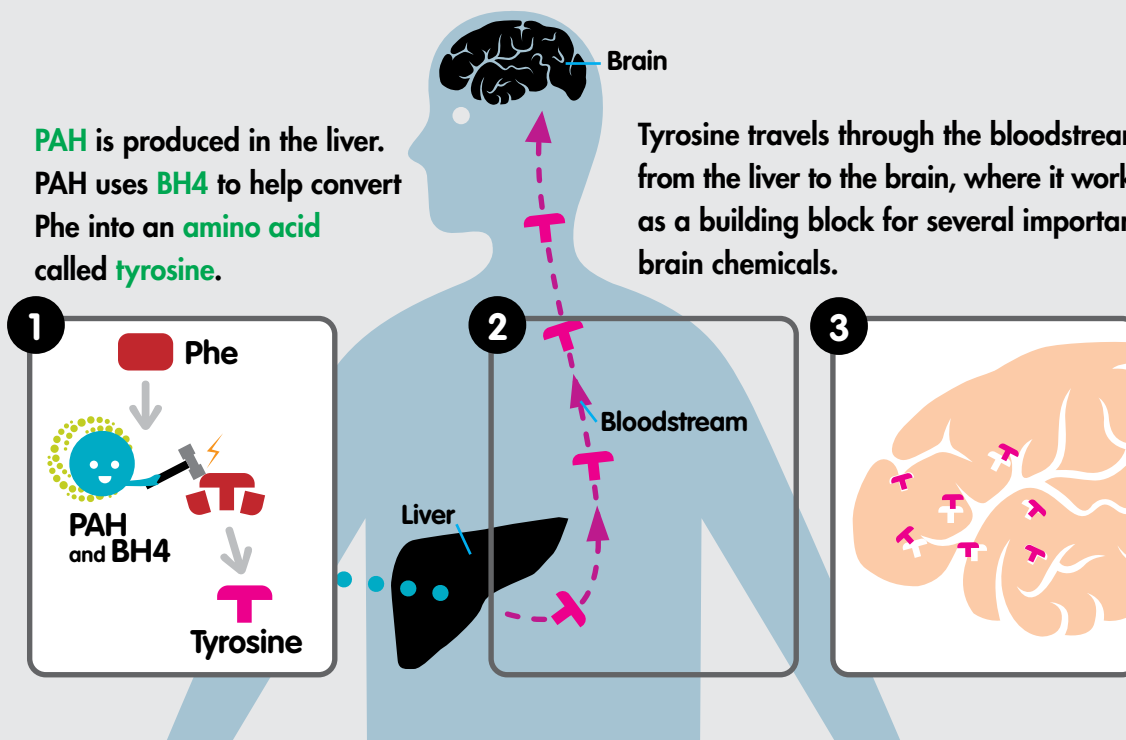
Lisa's daughter, Shayna, takes KUVAN



KUVAN helps protect your child from high Phe levels

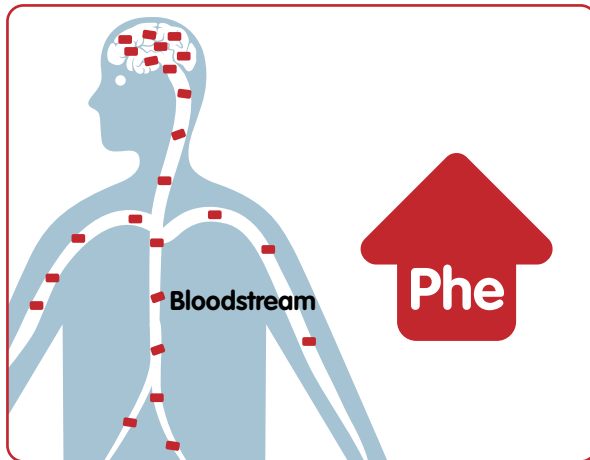
PAH is produced in the liver. PAH uses **BH4** to help convert Phe into an **amino acid** called **tyrosine**.

Tyrosine travels through the bloodstream from the liver to the brain, where it works as a building block for several important brain chemicals.



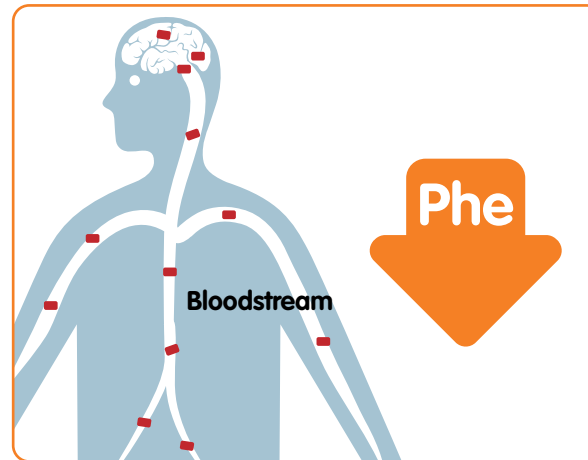
Words in GREEN are defined on the last page of this booklet.

Untreated PKU



In a child with PKU, Phe is NOT converted to tyrosine. If children with PKU do not follow a Phe-restricted diet, toxic levels of Phe can build up in the brain.

Treated PKU



KUVAN works with PAH in the body to help reduce Phe levels in the blood. KUVAN assists those with PKU by helping them stay at the target Phe level their doctor recommends.

Potential effects of untreated PKU

- Reduced IQ
- Seizures
- Impaired growth
- Mood and social problems

KUVAN was well studied in PKU patients

The health risks of not treating PKU are very high.

Staying safe and healthy can be a challenge with **PKU**. You must make smart choices in what your child eats and drinks. Making smart and safe choices in medicine is just as important.

BH4 has been used to treat PKU since the early 1990s.

In addition, the active ingredient in KUVAN, **BH4**, has been studied for 30 years in infants, children, and adults with PKU and other conditions.

The safety of KUVAN has been confirmed in multiple studies. In these studies, patients treated with KUVAN had about the same rate of side effects as patients who were treated with a placebo (a pill without any medicine in it).

The most common side effects reported were:

- Headache
- Diarrhea
- Abdominal (stomach) pain
- Throat pain
- Upper respiratory tract infections (like a cold)
- Vomiting and nausea

Similar rate of side effects in clinical trials

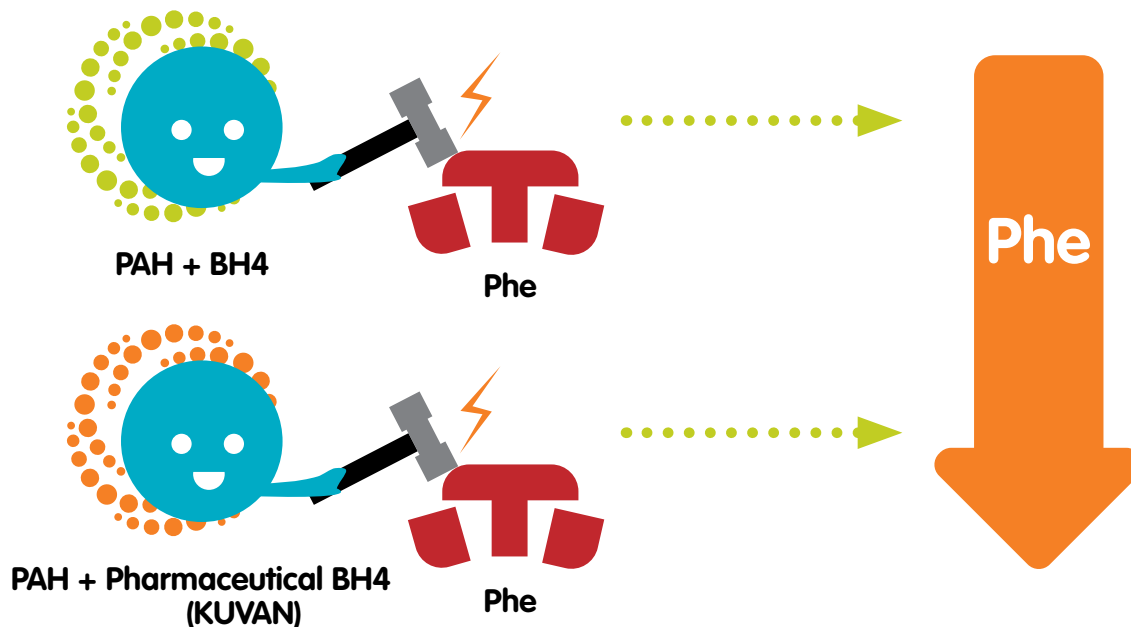
KUVAN

Placebo

Words in **GREEN** are defined on the last page of this booklet.

KUVAN is a pharmaceutical form of natural BH4

KUVAN works like natural BH4



BH4 is a natural substance found in the body. It helps reduce **Phe** to safe levels in the blood. The active ingredient in KUVAN is a synthetic version of BH4. It works the same way, by helping the **PAH** enzyme “wake up” and process Phe. This helps keep Phe levels in the blood low.

Safety studies for KUVAN and BH4



The safety of KUVAN has been confirmed in 579 patients with PKU for up to 30 weeks.⁵

In a 2-year study of PKU patients, KUVAN was shown to be well tolerated.⁵

Scientists have studied BH4, the active ingredient in KUVAN, for over 30 years. The safety of BH4 has been confirmed in many studies.

Two PKU studies in 2004 investigated the safety of BH4. In one, a 2-year study of children with PKU, BH4 was shown to be well tolerated.¹ The other study, in Japan, followed patients with PKU treated with BH4 for up to 4 years.² No serious side effects or treatment discontinuation related to BH4 were seen in either study.

In another study of young children with PKU, BH4 treatment was given for periods of up to 2 years with no reported serious side effects or treatment discontinuation.³



Finally, a 2005 study looked at the results of treatment with BH4 for up to 5 years. This study included children up to age 6. BH4 helped reduce Phe levels, with no reported serious side effects or treatment discontinuation.⁴

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Taking KUVAN Is Easy

KUVAN Tablets are taken:

- Once a day.
- At the same time each day.
- With food.

You will work with your doctor to determine how many KUVAN tablets are needed.



KUVAN can be mixed in apple juice and water

KUVAN can be mixed with 4–8 oz (1/2 – 1 cup) of water or apple juice until tablets dissolve.

- It may take a few minutes of stirring for the tablets to completely dissolve.
- Putting the tablets in a closed container and shaking it may result in the tablets dissolving more quickly.
- After the tablets dissolve, the liquid will appear cloudy, as in the photo and there may be small floating pieces. This is normal and safe for you to swallow. Drink the mixture within 15 minutes.
- Make sure you take all of the medicine in the glass. If any undissolved medicine remains in the glass, add 1–2 oz (1/4 cup or less) of water or apple juice and drink immediately.

A missed dose should be taken as soon as possible, but do not take 2 doses on the same day.

Remember, your diet should not be changed without the recommendation of your doctor or dietician.

BPPS—your help for KUVAN insurance coverage

Because KUVAN is the first treatment of its kind for PKU, BioMarin wants to make sure that your insurance company covers the cost of your KUVAN therapy. BioMarin Patient and Physician Support (BPPS) works with you and your health insurance company to help with coverage for KUVAN.

BPPS can also help you find insurance coverage if you do not have it already. To help make it easier, BPPS does most of the work and handles the details for you.

If you cannot afford your insurance co-payment, BPPS can help you work with the National Organization for Rare Disorders (NORD). This organization provides help with co-payments for eligible patients. NORD also provides financial help with insurance premiums, medical foods and formulas, and other costs related to KUVAN and PKU treatment.

If all other coverage options have been exhausted, BioMarin's Patient Assistance Program provides KUVAN at no charge to eligible patients.

Call today to learn more about how BPPS can help you.



877-695-8826
e-mail: bpps@BMRN.com



866-924-0100
www.rarediseases.org

3 ways to ensure your access to KUVAN

1

BPPS contacts your insurance company to confirm your coverage; it can also help you obtain coverage if you do not have it.

2

If you cannot afford your co-payment, NORD can provide financial assistance.

3

If you do not have insurance, or if your insurance does not cover KUVAN, the KUVAN Patient Assistance Program can provide KUVAN at no cost.

Words to know

Amino acid

A natural chemical that works as a building block for protein.

BH4

Tetrahydrobiopterin (also called BH4) is a naturally occurring chemical compound in the body. PAH needs BH4 to function properly.

PAH

Phenylalanine hydroxylase: An enzyme in the body that breaks down phenylalanine into tyrosine.

Phe

Phenylalanine (FEN-nil-ALA-neen): An amino acid found in many types of food.

PKU

Phenylketonuria (FEN-nil-KEE-toh-NOO-ree-ah): People with PKU can't get rid of Phe, an amino acid found in many foods, due to the PAH enzyme in their body that doesn't function properly. Having too much Phe in the body can harm the brain.

Sapropterin dihydrochloride

The generic (scientific) name for KUVAN.

Tyrosine

(TIE-roh-seen): An amino acid in the body that is used as a building block for several important brain chemicals.

References: **1.** Steinfeld R, Kohlschütter A, Ullrich K, Lukacs Z. Efficiency of long-term tetrahydrobiopterin monotherapy in phenylketonuria. *J Inherit Metab Dis.* 2004;27:449-453. **2.** Shintaku H, Kure S, Ohura T, et al. Long-term treatment and diagnosis of tetrahydrobiopterin-responsive hyperphenylalaninemia with a mutant phenylalanine hydroxylase gene. *Pediatr Res.* 2004;55:425-430. **3.** Hennermann JB, Bühler C, Blau N, Vetter B, Mönch E. Long-term treatment with tetrahydrobiopterin increases phenylalanine tolerance in children with severe phenotype of phenylketonuria. *Mol Genet Metab.* 2005;86(suppl 1):S86-S90. **4.** Trefz FK, Scheible D, Frauendienst-Egger G, Korall H, Blau N. Long-term treatment of patients with mild and classical phenylketonuria by tetrahydrobiopterin. *Mol Genet Metab.* 2005;86(suppl 1):S75-S80. **5.** Data on file, BioMarin Pharmaceutical Inc.



Helping you make smart choices for your child's health

This brochure provides facts about phenylketonuria (PKU) and KUVAN. KUVAN (sapropterin dihydrochloride) Tablets is approved to reduce blood Phe levels in patients with HPA due to BH4-responsive PKU. KUVAN is to be used with a Phe-restricted diet. If you have questions about KUVAN after reading this, talk to your child's doctor or dietitian to see if KUVAN is right for you.

Please see important safety information on the inside front cover, and read the enclosed patient package insert.

**Learn more about KUVAN by visiting www.KUVAN.com,
www.PKU.com, or by calling 1-877-MY-KUVAN (1-877-695-8826).**

HPA: hyperphenylalaninemia

BH4: tetrahydrobiopterin

PKU: phenylketonuria

B:OMARIN

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