

PKU, KUVAN, and You

PKU treatment and support for adults and young adults



An educational brochure brought to you by BioMarin Pharmaceutical Inc.


(sapropterin dihydrochloride) Tablets

Phe control—it's a lifelong goal!

Most young people with **PKU** learn how to manage a low-**Phe** diet with the help of their doctor, dietitian, parents, and other family members. But sticking to a low-Phe diet may become harder once you are older and are more independent.

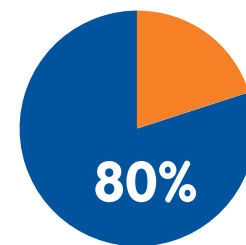
Your doctor has probably stressed that keeping your Phe levels low is an important way to help avoid problems with brain function. In fact, studies prove that PKU patients who keep lifelong control of their Phe levels do better in school and have fewer mental and physical problems.¹

Could it be more than just a bad mood?

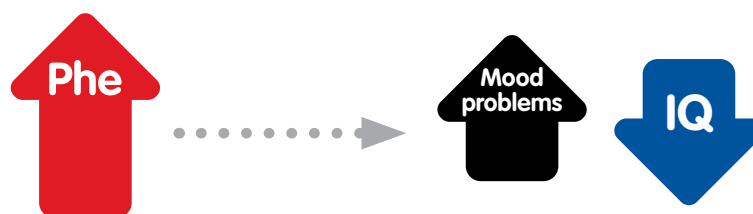
Unlike some childhood health problems, PKU is not something you outgrow. As an adult with PKU, you must continue to protect your health and brain function. When Phe levels are controlled, it's easier to think quickly and clearly. In contrast, high Phe levels can cause a person with PKU to feel sad, anxious, and confused.

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

Where do YOU fit in?



Surveys have shown that nearly 80% of teenagers with PKU fail to keep their Phe levels within the recommended range.²



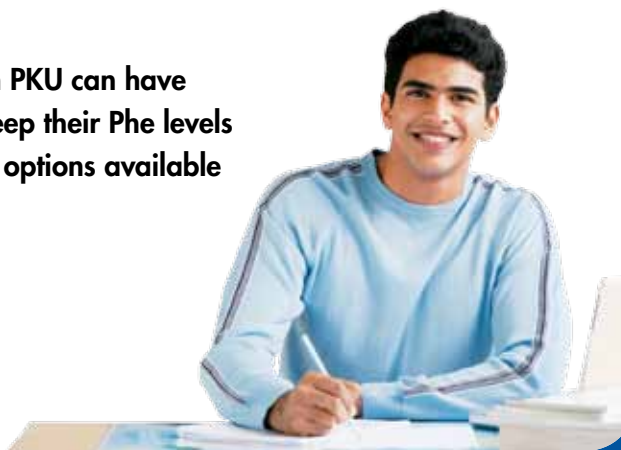
Over time, high Phe can lower your IQ. You could have problems finishing school or holding a job. To see if high Phe levels are affecting you, ask yourself the following questions:

Do I often have problems concentrating, solving problems, or finishing tasks?	YES	NO
Do I sometimes feel foggy or forgetful?	YES	NO
Am I often in a bad mood or crabby?	YES	NO
Do I often feel anxious or depressed?	YES	NO
Am I afraid to be around people?	YES	NO

If you can answer “yes” to one or more questions, it may be a sign that your Phe levels are too high.

Take control of your PKU

Don't let PKU hold you back! People with PKU can have great success in life—especially if they keep their Phe levels in control. Talk to your doctor about new options available for the treatment of PKU.



KUVAN—Extra help for living with PKU

The more you know about **PKU**, the better you can manage it. Staying safe and healthy can be a challenge. You must make smart choices in what you eat and drink. Making smart and safe choices in medicine is just as important. 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.

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Is KUVAN right for you?

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 lower your Phe levels and manage your PKU.



"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 taken once daily is also a major advantage."

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



Low-Phe diet

+ **KUVAN**[®] **=**
(sapropterin dihydrochloride) Tablets



Indication

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.

Please see important safety information on page 16, and read the enclosed patient package insert.

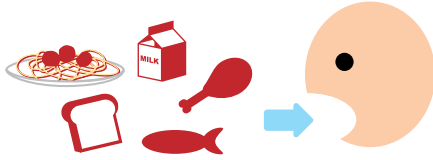
HPA: hyperphenylalaninemia

BH4: tetrahydrobiopterin

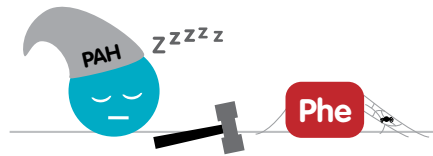
PKU: phenylketonuria

PKU: the Problem

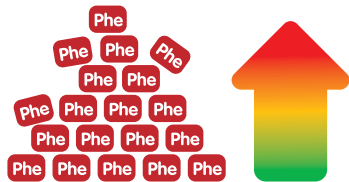
1 Phe is in most of the foods you eat



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



3 This leads to high Phe levels in the blood

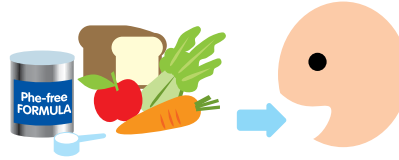


4 This can lead to problems in thinking and behavior



PKU: the Answer

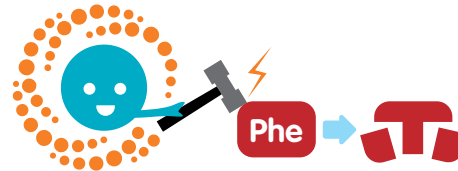
1 Follow a low-Phe diet



2 Take KUVAN once daily to find out if you respond



3 KUVAN stimulates PAH enzyme activity



4 Together, diet and KUVAN lower Phe levels



KUVAN works WITH your diet for better Phe control

KUVAN, used along with diet, can help some people with PKU reduce Phe levels in their blood more than 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. BH4 stimulates the PAH enzyme to begin breaking down Phe, thereby lowering Phe levels in the blood.

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

"As we all know, diet is tough. I have stayed on a controlled-Phe diet all my life, but it still can be challenging. KUVAN has been a motivator for me to stay proactive about my diet and keep my levels low."

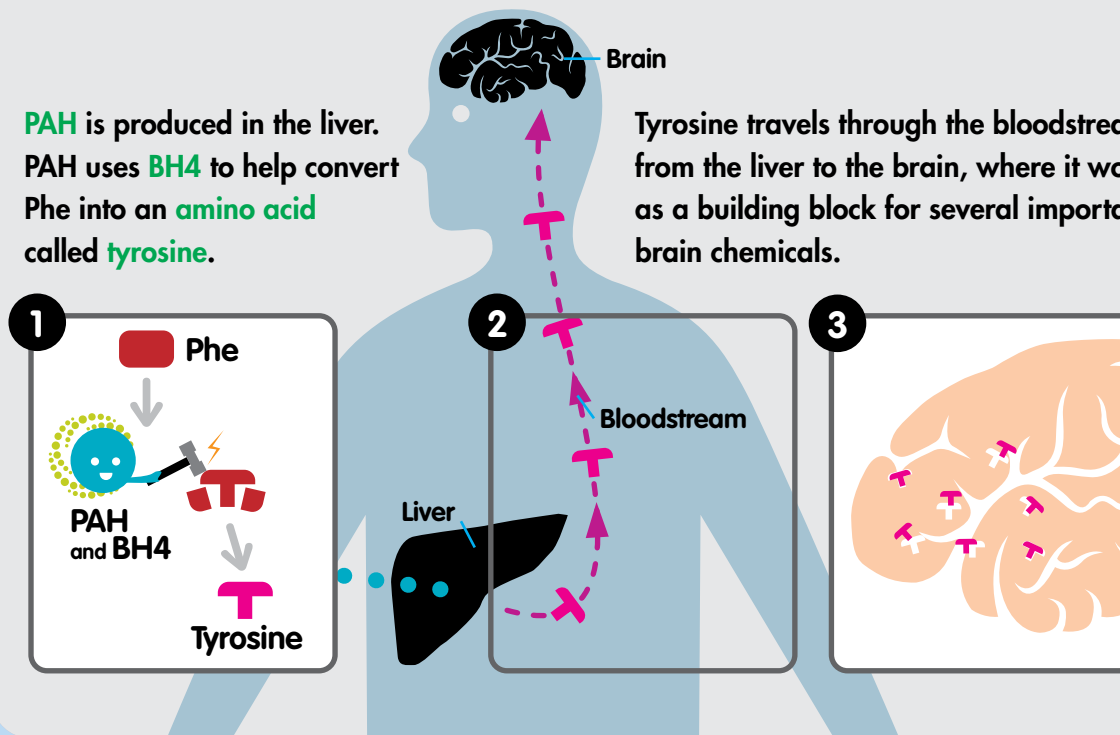
Julie takes KUVAN



KUVAN helps protect you from high Phe levels

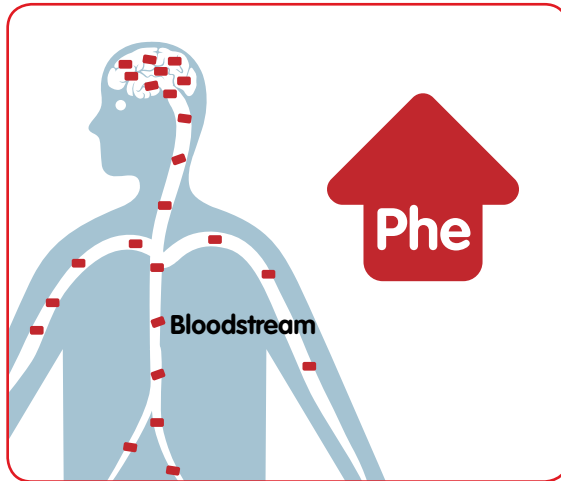
PAH is produced in the liver. PAH uses BH4 to help convert Phe into an amino acid called tyrosine.

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



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Untreated PKU

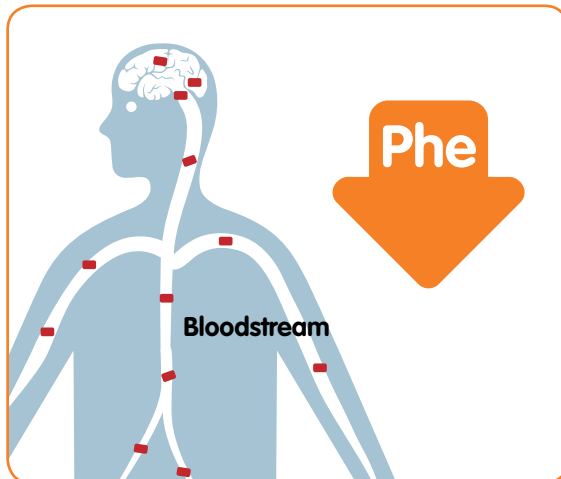


In a person with PKU, Phe builds up in the blood and is NOT converted to tyrosine. If people with PKU do not take steps to lower their Phe levels, toxic levels of Phe can build up in the brain and cause damage.

Potential effects of untreated PKU

- Reduced intelligence (IQ)
- Seizures
- Impaired growth
- Mood and social problems

Treated PKU

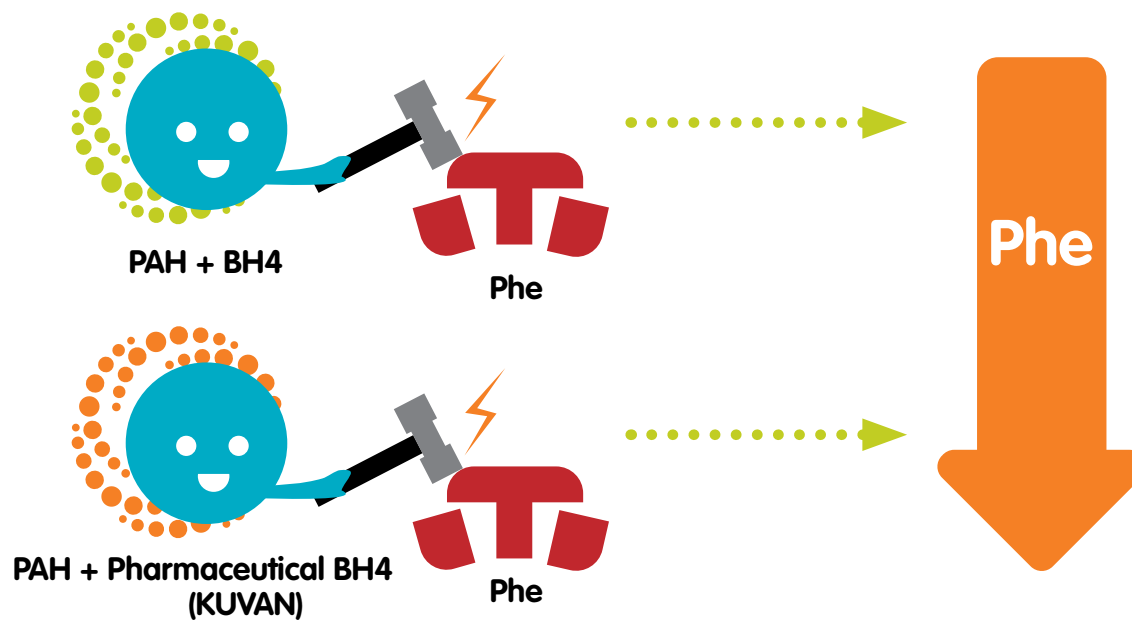


KUVAN works with PAH in the body to help reduce Phe buildup in the blood and lower Phe levels.

KUVAN is a pharmaceutical form of natural BH4

BH4, a natural substance found in the body, helps break down **Phe**. The active ingredient in KUVAN is a pharmaceutical 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.

KUVAN works like natural BH4



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The safety of KUVAN has been confirmed in many clinical trials



Prior to approval by the FDA in 2007, KUVAN was evaluated in a large number of patients with PKU in clinical trials. KUVAN was shown to lower Phe levels without a significant difference in side effects between the KUVAN-treated patients and those in the control (placebo) group.

KUVAN was also studied in a pre-FDA approval Expanded Access Program that provided access to nearly 400 patients who did not participate in the clinical trials.

As a part of the continued commitment to safety, a registry has been established for patients who have tried, are taking, or are about to begin KUVAN therapy.

Scientists have studied BH4, the active ingredient in KUVAN, for 30 years.

Kathleen takes KUVAN



Is KUVAN right for you?

KUVAN, the only FDA-approved prescription medicine for the treatment of PKU, has been available in the United States since 2007. For people with certain types of PKU, taking KUVAN has become an important way to help their bodies stay healthy.

How do you take KUVAN? Like many vitamins, KUVAN is taken daily. The number of KUVAN tablets taken depends on your weight. KUVAN is taken once a day, dissolved in water or apple juice.

What are the possible side effects of KUVAN?

Patients treated with KUVAN had about the same rate of side effects as patients treated with a placebo. The most common side effects reported were:

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



"I take KUVAN every day and it has helped me accomplish my treatment goals to better manage my Phe levels."

Gregg takes KUVAN

Thinking of starting a family?

Pregnant women should talk to their doctor before using KUVAN.
Here are some important facts about KUVAN and pregnancy:

It is very important to control Phe levels during pregnancy.

In studies of expectant women with PKU, high Phe levels were shown to harm the developing fetus. Therefore, low Phe levels are essential in reducing the potential for birth defects.

KUVAN has not been studied in pregnant women. KUVAN should be used during pregnancy only if it is clearly needed. If you are pregnant or plan to become pregnant, talk to your doctor before you start taking KUVAN.

If you decide to take KUVAN during pregnancy,
ask your doctor about enrolling in the KUVAN
Patient Registry.

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



National Organization
for Rare Disorders

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.

"After my doctor prescribed KUVAN, he had me sign two forms. A day or two later, I received a call from BPPS and was told that they would speak to my insurance company about coverage for KUVAN. Less than two weeks later, BPPS called and told me that my insurance company would cover KUVAN.

"Working with my case manager at BPPS was a breeze, and it was so nice to have someone else deal with my insurance company for a change."

Linda takes KUVAN



4 good reasons to consider Kuvan

KUVAN is covered by most insurance plans.

Because KUVAN is proven to work and benefit so many PKU patients, insurance coverage is excellent.

KUVAN is affordable.

Most patients have a co-payment of \$50 or less each month for their KUVAN prescription.

Financial assistance is available.

The KUVAN Patient Assistance Program provides KUVAN at no charge for eligible patients without insurance.

KUVAN puts better control in your hands.

KUVAN can help you control your Phe levels—and lower Phe means better outcomes.

KUVAN® (sapropterin dihydrochloride) Tablets is 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, 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 your diet and blood Phe levels 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 read the enclosed Patient Information.


(sapropterin dihydrochloride) Tablets

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.

Placebo

A medication with no active ingredient. It is given to patients in clinical drug studies to use in comparison with the effectiveness of the drug being studied.

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.** Koch R, Azen C, Friedman EG, Williamson ML. Paired comparisons between early treated PKU children and their matched sibling controls on intelligence and school achievement test results at eight years of age. *J Inherit Metab Dis.* 1984;7:86-90. **2.** Walter JH, White FJ, Hall SK, et al. How practical are recommendations for dietary control in phenylketonuria? *Lancet.* 2002;360:55-57.



Extra help for living with PKU

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.

Please see important safety information on page 16, and read the enclosed patient package insert.

Talk to your doctor or dietitian to see if KUVAN is right for you.

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

B:OMARIN

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