

BioMarin's Kuvan is First FDA-Approved Drug for PKU

In mid-December 2007, Kuvan™ (sapropterin dihydrochloride) was approved by the US Food and Drug Administration (FDA) for the treatment of tetrahydrobiopterin (BH4)-responsive PKU. Used in conjunction with a phenylalanine-restricted diet, the drug can help reduce blood phenylalanine (phe) in some people with PKU. Kuvan is a synthetic formulation of 6R-BH4, the cofactor for the enzyme missing in PKU (phenylalanine hydroxylase, or PAH). Kuvan can stimulate the activity of residual PAH enzyme so it metabolizes more phe to tyrosine. Kuvan comes in a 100 mg tablet that is taken by mouth anytime, once a day, with food (current research shows that it is best absorbed in tablet form, even though the label advises dissolving in water or juice). In clinical studies, Kuvan has been shown to be a safe treatment that reduces blood phe in some patients with PKU. To answer questions about the drug posed by National PKU News, the following information is provided.

Who Can Use Kuvan?

Individuals with a confirmed diagnosis of elevated phe due to PKU are eligible for Kuvan. There is no age restriction on the FDA-approved label; however, patients less than four years of age and older than 49 years of age were not studied with Kuvan. There are several reports of infants and young children who have been given BH4 for more than 2 years, but the numbers are small. These studies were conducted by Drs. Hennermann (1), and Steinfeld (2).

Can Pregnant Women Use Kuvan?

The use of Kuvan has not been clinically evaluated in pregnant women and should be used during pregnancy only if clearly needed. Women who are pregnant or planning to become pregnant should speak to their doctors before trying this medication.

By Elaina Jurecki, MS, RD, BioMarin Pharmaceutical Inc

High concentrations of phe are known to cause birth defects in children born to mothers with PKU. To-date, BioMarin is aware of a single reported case of maternal PKU successfully treated with BH4 and diet during pregnancy (3). There are 3 additional cases, soon to be reported, where BH4 was given to pregnant women with apparently good newborn outcomes. The use of BH4 in these cases has been discussed with the FDA, and informed consent was obtained since Kuvan had not yet been approved.

Women who take Kuvan during pregnancy are encouraged to enroll in the Kuvan patient registry. Call BioMarin Medical Information Services at 1-800-983-4587 for more information on the Kuvan Maternal Registry.

How Safe is Kuvan?

A total of 579 PKU patients have participated in clinical trials of Kuvan to-date, with 133 of these patients participating in placebo-controlled trials. The placebo-controlled trials were where Kuvan was compared to a placebo (a sugar pill) and administered in a blinded fashion so neither patient nor healthcare providers knew whether they were given drug or placebo. The most common side effects reported when using Kuvan were headache, diarrhea, abdominal pain, upper respiratory tract infection (like a cold), throat pain, vomiting, and nausea. The overall incidence of side effects in patients receiving Kuvan was similar to that reported with patients receiving placebo. Only one patient had to withdraw from the clinical studies early, due to a positive pregnancy test.

The most serious adverse reactions reported by investigators of their study subjects throughout the Kuvan clinical trials (regardless of whether they were receiving Kuvan or placebo treatment) were gastritis or stomach upset, spinal cord injury, streptococcal infection, testicular carcinoma, and urinary tract infection. (Note that any adverse reactions in clinical trials must be reported whether known

to be related or not to the drug being tested.) Mild to moderate neutropenia (low white blood count) was noted during Kuvan administration in 24 of 579 patients (4%). These adverse events were reported to occur during the study periods when the drug and placebo were being tested. There were no deaths.

Other studies have been conducted using an active ingredient similar to the one in Kuvan in various non-PKU patient populations to determine if it has any benefit in treating their underlying condition. Subjects with cardiovascular disease or neurological disorders were treated with sapropterin. Serious and severe adverse effects that occurred while these subjects were taking the medication have been included in the package information for Kuvan. It is unknown if these side effects were associated with the drug or the co-existing disease, but they were mainly attributed to the primary disease.

How Effective and Safe is Kuvan over the Long Term?

Based on BioMarin's clinical studies to-date, no loss of benefit was observed in patients taking Kuvan in a six-week study and a 26-week safety and efficacy extension study. Other formulations of BH4 have been used for over 25 years in patients with actual BH4 deficiency (not PKU) in Europe, and for several years in PKU in Europe and Japan.

Long-term use of BH4 for treatment of patients with PKU has been described by a few other investigators. Cumulative daily doses of BH4

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For a another view on Kuvan, please see "The FDA Should Not Have Approved Kuvan," on page 3.

ranging from 1.7 to 20 mg/kg/day have been used for 3 months or longer (up to 56 months) in 9 children. A total of 24 cases are described in published studies by Drs. Steinfeld, Shintaku, Trefz, and Blau (2, 4, 5, 6, 7). These children were reported to have normal physical and mental development on BH4 therapy.

More than 50 US metabolic centers and 400 individuals with PKU were able to participate in BioMarin's Expanded Access Program, before FDA approval of Kuvan. Approximately 50% of patients have remained on Kuvan after the response testing period with the remainder dropping off for non-responsiveness, non-compliance, or side effects. BioMarin believes that most of these side effects were not related to taking Kuvan; only two subjects withdrew, due to gastrointestinal problems. These subjects took Kuvan on an empty stomach. Further investigation showed that the drug was better tolerated and absorbed when taken with food.

How Might the Diet Change with Kuvan Use?

Since changes in dietary phe intake can obscure or override the effect of Kuvan on blood phe levels, and because not all individuals will respond to the drug, people with PKU should be treated with a phe-restricted diet in addition to treatment with Kuvan. People starting on Kuvan need to maintain a consistent diet and lifestyle. They should work closely with their dietitian, who can assist them in adjusting their diets to maintain their blood phe in the therapeutic range and ensure an adequate nutrient intake. Guidelines to assist metabolic dietitians in managing the diets of persons taking Kuvan will be published this spring in the scientific journal, *Topics in Clinical Nutrition*.

In the series of clinical trials sponsored by BioMarin, one was designed to evaluate the ability of Kuvan, at a dose of 20 mg/kg/day, to increase phe tolerance while maintaining adequate control of blood phe in children with PKU who were simultaneously being treated with a phe-restricted diet.

Out of a larger sample, the children (ages 4 to 12) who were found to be responsive to Kuvan received either Kuvan 20 mg/kg/day (33 children) or placebo (12 children) for 10 weeks while maintaining a phe-restricted diet. After the third week of treatment, children received phe supplements (nonfat milk powder or egg powder added to their formula) when their blood phe was found to be below 6 mg/dl (360 µmol/L). After ten weeks, the amount

of phe supplemented in the Kuvan group had increased an average of 20.9 mg/kg/day (± 15.4 mg/kg/day) from the beginning of the study, while maintaining blood phe control less than 6 mg/dl (360 µmol/L). In contrast, the average increase in phe supplementation in the placebo group was only 2.9 mg/kg/day (± 4 mg/kg/day). There were no severe adverse events related to Kuvan treatment and no adverse events leading to early withdrawal from the study. Study results will be published this spring in *Journal of Pediatrics*.

How was Kuvan Pricing Determined and How Will Insurance Coverage Work?

Setting the appropriate price is very challenging for breakthrough, one-of-a-kind drugs developed to treat rare diseases. The price of Kuvan is consistent with other unique drugs that address small populations with high, unmet medical needs. Health care insurance companies or "the payers" understand this and have demonstrated a nearly universal willingness to provide drug benefit coverage for Kuvan. The drug could be viewed as an "ultra-orphan" medicine since there are a very limited number of patients who will take it.

Our initial cost estimate for Kuvan was determined by examining our clinical trial experience to arrive at the average patient drug cost to the insurance company payers of \$57,000 per year. This was based on the average patient weighing 99 lbs. (45 kg), taking an average dose of 15 mg/kg/day (mid-point of the recommended starting dose and maximum dose) and a compliance rate of 80% (people in general don't usually take 100% of the drug they are prescribed). The cost of one 100 mg tablet is currently \$29. BioMarin acknowledges that some patients are larger than our "average" patient and will end up taking the maximum 20 mg/kg/day dose to control their blood phe. In these situations, the monthly cost of Kuvan will be significantly more than the estimated average. (editor's note: for example, for an adult weighing 150 pounds, using the maximum dose, and 100% compliant, the cost would be \$144,000 per year).

BioMarin has made important long-term commitments to the PKU community based on the fundamental promise that no patient will be denied access to Kuvan for lack of insurance or ability to meet co-pays. As such, the company has set up the BioMarin Physician and Patient Support program (BPPS). Revenues from sales of Kuvan will fund the programs outlined here:

► **For patients with prescription drug coverage.** BPPS can help with Kuvan coverage by conducting benefit investigations, authorizations,

and appeals, as well as engaging in other communications.

► **For patients who cannot afford co-payments.** BPPS can refer you to the National Organization for Rare Diseases (NORD) program for financial assistance. Drug co-pays of any size are eligible for consideration of NORD's assistance. This is a new program offered by NORD, and early on there were some delays with implementing services. However, this program is now fully functional and NORD is committed to acting as an advocate for the patient in providing support.

► **For patients with no insurance coverage.** BPPS can help you find insurance coverage. If coverage can't be found, BPPS can refer you to the patient assistance program (PAP) for "compassionate use" drug (provided free of charge by BioMarin) while BPPS continues to work to find healthcare coverage with prescription drug benefits.

Because Kuvan is an FDA-approved drug, insurance companies generally cover prescription drugs when used within the FDA-approved indication and this has been true of Kuvan. They may deny medical formula or other products that don't fit so neatly into the prescription category. Typical monthly co-pays have been in the range of \$30-\$50, but co-pays can vary widely. If a co-pay is substantial enough to create a financial burden for the patient, the patient is referred to NORD's financial assistance program.

BPPS has added customer service, reimbursement, and case management staff in order to accommodate the many calls we have received. BPPS apologizes for past patient inconveniences, but the added customer service staff has improved responsiveness and shortened timelines for patients beginning Kuvan.

The time it takes for insurance to verify coverage varies. If a prior authorization is required, it may take weeks or even a month or more. It is reasonable to expect that on average, it will take 2 to 4 weeks to complete the insurance investigation and for the patient to receive Kuvan. For patients who will exceed their insurance "caps" in paying for Kuvan, BPPS is referring patients to NORD or BioMarin patient access programs to seek alternate insurance programs or financial assistance.

For more information on BioMarin Physician and Patient Services, please contact BPPS at 1-877-MY-KUVAN (1-877-695-8826) or bpps@BMRN.com. More information on Kuvan, as well as the package insert, can be found on the website: www.Kuvan.com.

BioMarin's Future Plans

► **Investigational studies.** BioMarin will begin conducting a long-term study to assess the impact of Kuvan on neurocognitive function in children with PKU, 0 to 8 years of age. BioMarin is also supporting studies conducted by independent investigators on various aspects of Kuvan therapy in PKU patients.

► **PKU registry.** The registry is to provide a way for physicians, the FDA, and BioMarin to monitor the safety and effectiveness of Kuvan over a long period of time in as many patients as possible. There also will be a registry for maternal PKU patients.

► **PEG-PAL therapy.** BioMarin has an investigational product in development called PEG-PAL (an enzyme substitution product), which will potentially be useful to treat a broader range of PKU patients.

► **Medical formula assistance program.** In recognition of the importance of the phe-restricted diet for all PKU patients, BioMarin has provided a grant to NORD for a financial assistance program for PKU medical formula (this is a Kuvan-independent program offering). This exciting program is in final planning stages and should be available soon.

► **Home blood phe monitoring device.** BioMarin is investing in the development of a home blood phe monitoring device.

► **Kuvan Dietitian Information (KDI) Services.** KDI Services is a hotline for healthcare providers that offers access to expert dietitians who have experience with nutritional management of patients taking Kuvan. Access this service through BioMarin's Medical Information Services.

► **National PKU Alliance.** BioMarin hosted a PKU Community Summit meeting last year and will host two additional meetings this year to help facilitate the development of a national PKU parent organization.

References

- 1) Hennermann JB, Bühner C, Blau N, et al. Long-term treatment with tetrahydrobiopterin increases phenylalanine tolerance in children with severe phenotype of phenylketonuria. *Mol Genet Metab* 2005; 86 (suppl 1):S86-90.
- 2) Steinfeld R, Kohlschütter A, Ullrich K, Lukacs Z. Efficacy of long-term tetrahydrobiopterin monotherapy in phenylketonuria. *J Inher Metab Dis* 2004; 27:449-53.
- 3) Koch R, Moseley K, Guttler F. Tetrahydrobiopterin and maternal PKU. *Mol Genet Metab* 2005; 86:S139-41.
- 4) Shintaku H, Kure S, Ohura T, et al. Diagnosis and long-term treatment of tetrahydrobiopterin-responsive hyperphenylalaninemia with a mutant phenylalanine hydroxylase gene. *J Inher Metab Dis* 2003; 26 (suppl 2).
- 5) Trefz FK, Aulela-Scholz C, Blau N. Successful treatment of phenylketonuria with tetrahydrobiopterin. *Eur J Pediatr* 2001; 160:315.

6) Blau N, Bernegger C, Trefz FK. Tetrahydrobiopterin-responsive hyperphenylalaninaemia due to homozygous mutations in the phenylalanine hydroxylase gene. *Eur J Pediatr* 2003; 162:196.

7) Steinfeld R, Kohlschütter A, Zschocke J, et al. Tetrahydrobiopterin monotherapy for phenylketonuria patients with common mild mutations. *Eur J Pediatr* 2002; 161:403-405.

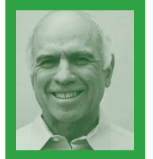
The FDA Should Not Have Approved Kuvan

by Dr. Richard Kronmal, PhD, Seattle, WA, and Dr. Larry Sasich, PharmD, MPH, FASHP, Erie, PA

In the Fall 2007 newsletter, as your editor, I wrote a piece entitled Should I try the New Drug? Weighing Risks vs. Benefits. There, I outlined my concerns about Kuvan, in advance of its FDA approval. My major point was that everyone considering the drug needs to weigh the risks versus the benefits for their own unique circumstances. (Read the entire editorial at www.pkunews.org in the Research section.)

With the PKU community's high interest in the drug, I thought it would be worthwhile to have two outside scientists comment on the data reviewed by the FDA that led to Kuvan's approval in December 2007. Their editorial will surprise you. It may make you (and your clinic) think even more carefully about using the drug than you would have otherwise.

The two scientists are a nationally known expert in clinical trials, biostatistician Dr. Richard Kronmal; and a pharmacist with extensive knowledge of drugs and the FDA drug approval process, Dr. Larry Sasich. Dr. Kronmal is my husband; I could think of no one better to make comments on the subject of drugs and clinical trials since his entire professional life, more than four decades, has been devoted to medical research through clinical trials at the University of Washington. He has extensive experience with the FDA and the drug approval process, serving on an FDA Advisory Committee for four years. He also has served as a consultant to drug companies and has been (and continues to be) a member of many Data Safety Monitoring Boards for drug companies. Finally, he has a long history of involvement with PKU research as a biostatistical consultant both to the large National Collaborative Study of Children Treated for PKU and the International Maternal PKU Collaborative Study.



Dr. Richard Kronmal



Dr. Larry Sasich

Dr. Kronmal collaborated on this editorial with Dr. Larry Sasich, PharmD, MPH, FASHP, of the LECOM School of Pharmacy. Dr. Sasich worked for 10 years as a research analyst at Public Citizen's Health Research Group in Washington, DC before assuming his current role as a professor of pharmacy. His major responsibilities were related to issues involving the FDA, access to drug information for consumers, drug safety, and the cost of prescription drugs. He is the co-author of Worst Pills, Best Pills and for 12 years was the primary contributor to Worst Pills, Best Pills News, a newsletter written for consumers
—Virginia Schuett, MS, RD, editor

When a patient or the parent of a patient is considering use of a new drug, four factors come into play: (1) comparative effectiveness (is the new drug better than existing drug or non-drug therapies?); (2) efficacy; (3) safety; and (4) cost. Certainly, the high cost of Kuvan is an issue, but not one that we will deal with here.

Throughout this editorial we will refer to the FDA review documents that resulted in the approval of Kuvan (also referred to as sapropterin) for the treatment of PKU. All quotations come from these documents, which are available on the FDA web site at <http://www.fda.gov/cder/foi/nda/2007/022181TOC.htm>. These documents are rigorous reviews of data and clinical trials submitted by BioMarin to support Kuvan approval.

The PKU Diet

The development of the PKU diet, a highly effective and very safe treatment for PKU, is one of the major medical achievements of the

twentieth century. At the time the diet was developed there was a clear and compelling need for a treatment because untreated PKU resulted in mental retardation and other neurological problems. One only has to read the stories of the Guthrie Scholarship winners in this newsletter to appreciate the success of diet treatment. The PKU diet also has been shown to be very safe. After over 40 years of use there are no known serious adverse effects from the diet. Thus, we might ask, is there a need for a new treatment and would a new treatment be a useful addition to diet?

What is the Need for Kuvan?

In support of the need for Kuvan, the FDA summary of their overall review states: "Compliance with diet, especially in older children, adolescents, and adults, is difficult, and non-compliance at older ages is almost universal. Barriers to adherence include economic, psychosocial, and health care