

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

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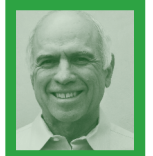
The FDA Should Not Have Approved Kuvan

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

system issues. Thus, new treatments for PKU are clearly needed.”

We believe this premise is partially false. While there is no survey data available on the degree of non-compliance with diet, anyone who reads this newsletter or participates in the PKU list serve group knows that there are many children, adolescents, and adults with PKU who are, in fact, fully compliant with the diet and plan to remain so for their entire life. Still there is no denying that maintaining the diet is difficult for some and there are many with PKU who are non-compliant or poorly compliant. However, we believe that Kuvan will not solve (and may make worse) the economic issues referred to by the FDA due to its high cost and the considerable uncertainty concerning lifelong insurance coverage of these costs. Nor is there any certainty that for most people, a “relaxed” diet that may be followed on Kuvan will solve the psychosocial or health care system issues that lead to lack of blood phe control in the first place.

In other portions of their review, the FDA states, “*There is no blood phe level below which normal neurocognitive development is assured,*” and suggests that the risk of “neurocognitive impairment” is still present for those under good control. While the FDA clearly believed this to be true, and used this as part of their rationale for Kuvan’s “need” and for the urgency of its approval, there is no documented evidence showing that children or others who maintain excellent blood phe control are at risk for “neurocognitive impairment.”

What is the Benefit (Efficacy) of Taking Kuvan?

In setting the standard on which the efficacy of Kuvan was to be judged, the FDA agreed to the proposal by Biomarin that: “blood phe levels would be an acceptable primary endpoint in clinical studies submitted in the NDA” (NDA =New Drug Application); however, Biomarin was required also to submit a plan for post-approval follow-up of treated patients to assess long-term potential benefits of treatment (for example, long-term clinical endpoints such as IQ and neuropsychological status).”

“Surrogate Endpoints” and Kuvan

An endpoint such as blood phe levels is termed a “surrogate” (substitute) endpoint. That is, it is a measure that is *associated with* important clinical endpoints (in this case, IQ) but is *not an entirely satisfactory measure*

of the effect of the drug on the endpoints that are important to the patient, such as IQ and neuropsychological status. This is the reason the FDA required that BioMarin submit a plan for post-approval studies of the effect of Kuvan on clinically important endpoints.

The FDA policy of allowing the approval of drugs based on surrogate endpoints has recently come under considerable criticism due to examples where a drug had beneficial effects on the surrogate endpoint but was harmful to the patient. Recently, the FDA has not been accepting the use of surrogate endpoints, and instead has required pharmaceutical firms to show efficacy for clinically meaningful endpoints. For example, the FDA now requires studies in Cystic Fibrosis (CF) patients to show that any new antibiotics decrease hospitalization and/or use of intravenous antibiotics rather than simply requiring that the studies show an improvement in lung function.

We do not agree with the FDA’s acceptance that a positive effect of Kuvan on blood phe levels was sufficient for determining approval of the drug. Historically, the requirement for post-approval studies has not been a successful strategy for determining either the clinical efficacy or safety of drugs. This policy has failed for multiple reasons. First, the FDA has been extremely lax in forcing compliance of the drug firms to this requirement. Second, the drug companies have little incentive to do these studies in a timely fashion or to do them well. Third, once the drug is on the market and widely used it is very difficult to get patients to enroll in a study of the drug compared to the alternative treatment. Because of these factors, it often takes many years before it is discovered that a drug in wide use is either ineffective or unsafe.

We believe that the FDA should have required studies of sufficient size and duration to evaluate the effect of Kuvan on intellectual development and neuropsychological status (as well as on long-term blood phe control) *before*, not after, approval. These studies would have probably required several hundred subjects and several years of follow-up; but only studies of this kind can provide the information necessary to judge the true efficacy (and safety) of Kuvan.

BioMarin’s Clinical Trials

BioMarin’s studies have shown that Kuvan modestly lowers blood phe levels in carefully controlled circumstances in some patients. The primary study demonstrating declines in phe levels began with 489 patients who were not on diet treatment. After 8 days of treatment with Kuvan, the average decrease in phe levels was only 10%. Ninety-six patients were considered “responders” based on criteria of at least a 30% drop in phe levels after 8 days of treatment. Noteworthy is the fact that patients with blood phe greater than 10 mg/dl (>600 µmol/L) at the start of the study were less likely to respond to treatment (15% of 428 patients) than were patients with blood phe less than 10 mg/dl (<600 µmol/L) at the start of the study (54% of 57 patients). This is important for two reasons.

First, it shows that among PKU patients who have elevated phe levels, few respond to Kuvan. Second, the impact of taking Kuvan on phe levels of patients with levels below 10 mg/dl (<600 µmol/l) may be a relatively small change in their phe levels (for example, a 30% drop from 10 mg/dl is only 3 mg/dl or 180 µmol/L).

This screening study was followed by a randomized

study in which, of the 96 “responders,” 41 patients were assigned to Kuvan and 45 to a placebo for an 8-week period. This study provided convincing evidence that Kuvan lowers phe levels in “responders” by about 32% compared to placebo at a 10 mg/kg dose.

In the next study (PKU-004, an extension of the previous screening study) the FDA summarized the finding: “Thus, the overall results for PKU-004 show a clear dose-response effect of sapropterin (Kuvan) on blood phe levels in patients with BH4-responsive PKU, with statistically significant differences in mean change in blood phe levels seen between the different dosage levels (5, 10, and 20 mg/kg/day). The results also show that the effect of sapropterin treatment on blood phe levels was sustained throughout the 22-week treatment period of the study.”

The final clinical study in support of the new drug application for Kuvan began with 90 patients who were in good dietary control (phe level of less than 8 mg/dl or 480 µmol/L). It is the only one of the clinical trials to study

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children from ages 4 to 8 and the only one to look at subjects in good diet control. These patients were all given Kuvan for a period of 8 days, at a 20 mg/kg dose. “Responders” were defined as patients who at Day 8 had a decrease in blood phe of at least 30% from their pretreatment level and had a blood phe level of less than 5mg/dl (<300 μmol/L) on that day. Fifty of these patients were “responders” by these criteria; 45 of them went on to the second phase of the study in which ¾ (33 patients) were treated with Kuvan and ¼ (12 patients) received a placebo.

This second phase of the study tested the effect of increasing dietary phe on blood phe levels in those on Kuvan compared to those taking placebo: “The sapropterin group tolerated a mean dietary phe supplement of 21 mg/kg/day at Week 10, which was significantly different for the pre-treatment amount of zero supplement (p<0.001). This amount was also significantly greater than the amount tolerated by the placebo group of 3 mg/kg/day.”

Two other small studies were undertaken to determine when and how often the drug needs to be taken. **However, these studies were inadequate, and the data are insufficient to support a once a day regimen for Kuvan.**

Kuvan is Not Approved for Liberalizing the Diet

The FDA went on to comment about the final major clinical trial: “The outcome measure of increased dietary phe tolerance is problematic. An increase in dietary phe tolerance is not an accepted endpoint for PKU, and the relevance of this short term endpoint as an indicator of a clinically meaningful benefit in PKU has not been demonstrated. In addition, the safety of increased phe tolerance with sapropterin treatment on neurocognitive development has not been established, and could only be established by a long-term neurocognitive study (i.e., over several years).”

The FDA reviewer concludes the report with the following important statement: “**Both Reviewers also found that there is insufficient data to indicate a change in diet for PKU patients receiving Kuvan treatment.**” In other words, even if Kuvan is added to the diet there is not enough evidence to support modifying the PKU diet in those taking the drug. Clinical data *only* supports Kuvan being added to the current PKU diet to decrease inadequately

controlled phe levels and *not* as a means to liberalize the diet.

Do We Know that Kuvan is Safe?

The most important issue in evaluating the safety data for Kuvan is the small number of patients treated in controlled studies.

Controlled studies are the standard by which new drugs are evaluated.

Clinical data only supports Kuvan being added to the current PKU diet to decrease inadequately controlled phe levels and not as a means to liberalize the diet.

The FDA summary of BioMarin’s Kuvan trials reports that there were only 74 Kuvan and 59 placebo patients in controlled trials. Further, the maximum length of these trials was only 22 weeks. For a drug that will be used chronically, possibly over a lifetime, this very limited and short-term data provide little reassurance that Kuvan’s safety is known.

The FDA medical reviewer concludes, “. . . duration of exposure was not adequate to support long-term safety.” Even with this limited experience there are reasons to be cautious about Kuvan use. Specifically, the FDA noted that 4% of patients in Kuvan trials experienced neutropenia (low count of a type of white blood cell) and mandated “the risk of neutropenia is to be addressed prominently in labeling” (but its mention on the labeling is hardly “prominent”). Neutropenia places the person at higher risk for infections of all kinds. It is uncertain, given the small number of cases and in many instances the lack of controls, whether this side effect was due to Kuvan or whether it is of medical importance. On the other hand, there were 3 serious adverse events in those taking Kuvan compared to 1 in placebo patients that were infection-related (a case of acute appendicitis, a urinary tract infection, and a streptococcal pharyngitis or severe sore throat). Interestingly, there were more minor sore throats reported in the Kuvan group than in the placebo group. Again, whether these side effects are due to Kuvan is not known and they may or may not be serious. **Nonetheless, we believe routine monitoring of white blood counts should be done for anyone on the drug.**

While blood pressure was monitored in at least some of the Kuvan trials, the FDA report includes no actual data on changes in blood pressure. Kuvan is being tested in adults with severe hypertension to determine if it can be used as a treatment to lower blood pressure. (There are biological reasons to believe that Kuvan will lower blood pressure.) This potentially could be of concern, particularly in

healthy children. Decreases in blood pressure can result in dizziness and headaches and over the long term might have adverse cardiovascular effects. The lack of data presented makes it impossible to evaluate the potential of Kuvan to have adverse effects on blood pressure regulation.

One final important issue is the lack of safety data on children under 8 years of age. **Only 24 children between ages 4 and 8 years were included in the single study of Kuvan in the younger age group (and some of these were in the placebo group not receiving Kuvan), lasting just 10 weeks.** This limited number of patients and short time is completely inadequate to assess even short term safety. Because children break down and eliminate drugs differently than adults, one cannot extrapolate data for young children based on results in older children or adults.

Conclusion

Many of you have been told by physicians or by BioMarin that Kuvan is both safe and effective. We don’t agree with this assessment based on the clinical trial data. Further, the widespread adoption of Kuvan among the PKU community as a means to “liberalize” the diet (which the FDA clearly and explicitly rejected as a recommended use for Kuvan) may not ultimately result in better control of blood phe or the intended major outcome of better cognitive functioning. The introduction of higher protein foods may actually result in poorer compliance with the diet (or even its abandonment) as the patient becomes used to eating these foods. And will the brain be as protected by Kuvan as by diet restriction of phe? No one knows. Also, we do not know if Kuvan will lose its effectiveness with long term use.

In summary, use of Kuvan has not been shown to prevent the adverse neurological outcomes associated with PKU in even one clinical trial, while dietary restriction of phenylalanine has been shown to be extremely effective. Neither has Kuvan been shown to be safe. The drug has been tested in short term studies in a small number of patients and none younger than 4 years of age. Clearly the long term safety of the drug remains to be established.

Before using any drug you should be aware that all drugs come with both risks and benefits. It is unlikely that they will have only benefits. Also, consider that many drugs are used for short periods of time and thus the risks can be determined (and the risks are often low for such short term use). On the other hand, Kuvan may be started in childhood and used for a lifetime, and yet it could be decades before we learn if the drug is safe.