

Compound: Kuvan from BioMarin (BMRN)
Indication: Phenylketonuria (PKU)
Status: Commercial/Approved
Featured Expert: **Barbara Burton, MD**

Discussion Topic:

BioMarin's Kuvan was approved by the FDA as the first, and currently the only, prescription drug therapy for the treatment of PKU. Kuvan is proven to reduce blood Phe levels in patients with hyperphenylalaninemia (HPA) due to BH4-responsive PKU, and is to be used in conjunction with a Phe-restricted diet.

With our expert, Dr. Barbara Burton, we will discuss how Kuvan is impacting the standards of care for PKU patients as well as the key clinical, safety and commercial drivers and challenges within the PKU setting.

Background – Phenylketonuria (PKU)

PKU is an inherited, genetic condition in which the body is not able to process phenylalanine (Phe), an amino acid found in many foods. PKU is caused by a defect in the enzyme in the body that works to process Phe. This enzyme is called phenylalanine hydroxylase (PAH). In order for the PAH enzyme to work, it needs BH4, a molecule that is naturally present in the body. When the PAH enzyme is defective, the Phe concentration then builds up inside the body in the bloodstream, eventually passing into the brain

It is well known that unmanaged PKU likely causes severe mental retardation, delayed mental development, seizures, tremors, spasticity, difficulties in executive functioning, behavioral issues, irritability, and eczema in childhood. However, the exact mechanism by which it occurs is not well known. While gray matter atrophy and reduced dendritic arborization have been observed, MRI studies have revealed another notable neuropathological finding: diffuse white matter abnormalities. These include delayed or defective myelination, status spongiosis, demyelination, and gliosis. Additional studies have observed abnormal cerebrospinal fluid neurotransmitter concentrations.

The incidence of PKU is about 1 in 15,000 births worldwide, but the incidence varies widely in different human populations from 1 in 4,500 births among the population of Ireland to fewer than one in 100,000 births among the population of Finland. In the US it is estimated that at least 1 baby in 25,000 is born with PKU. Every state in the US now screens infants for PKU at about 3 days of age. BioMarin estimates the current in-clinic patient population in the US to be approximately 7,400 with 50,000 diagnosed patients under the age of 40 in the developed world.

In 2000, the National Institutes of Health (NIH) convened a panel of experts who decided that lifelong care is required for the treatment of PKU. This decision settled the debate about how long people with PKU should remain on the Phe-restricted diet. Based on this decision, the management approach has come to be known as “diet for life.”

Clinical Development Overview

BioMarin's Kuvan (sapropterin dihydrochloride) Tablets are indicated in the United States 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. The active ingredient in Kuvan, sapropterin dihydrochloride, is the synthetic form of 6R-BH4 (tetrahydrobiopterin), a naturally occurring enzyme cofactor that works in conjunction with phenylalanine hydroxylase (PAH) to metabolize Phe.

Kuvan has received orphan drug designation from both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Kuvan has received seven years of orphan exclusivity in the United States and ten years of market exclusivity in the E.U.

Clinical Trial Study Results

The efficacy and safety of Kuvan were evaluated in four clinical studies in patients with PKU.

Study 1 -- A multicenter, open-label, uncontrolled clinical trial of 489 patients with PKU, ages 8 to 48 years (mean 22 years), who had baseline blood Phe levels greater than or equal to 450 umol/L and who were not on Phe-restricted diets. All patients received treatment with Kuvan 10 mg/kg/day for 8 days. Response to Kuvan treatment was defined as a greater than or equal to 30% decrease in blood Phe from baseline. Results: At Day 8, 96 patients (20%) were identified as responders.

Study 2 -- A multicenter, double-blind, placebo-controlled study of 88 patients with PKU who responded to Kuvan in Study 1. After a washout period from Study 1, patients were randomized equally to either Kuvan 10 mg/kg/day (N=41) or placebo (N=47) for 6 weeks. Efficacy was assessed by the mean change in blood Phe level from baseline to Week 6 in the Kuvan-treated group as compared to the mean change in the placebo group. Results: At baseline, the mean (+/-SD) blood Phe level was 843 (+/-300) umol/L in the Kuvan-treated group and 888 (+/-323) umol/L in the placebo group. At Week 6, the Kuvan-treated group had a mean (+/-SD) blood Phe level of 607 (+/-377) umol/L, and the placebo group had a mean blood Phe level of 891 (+/-348) umol/L. At Week 6, the Kuvan- and placebo-treated groups had mean changes in blood Phe level of -239 and 6 umol/L, respectively (mean percent changes of -29% (+/-32) and 3% (+/-33), respectively). The difference between the groups was statistically significant ($p < 0.001$). Change in blood Phe was noted in the Kuvan-treated group at Week 1 and sustained through Week 6.

Study 3 -- A multicenter, open-label, extension study in which 80 patients who responded to Kuvan treatment in Study 1 and completed Study 2 underwent 6 weeks of forced dose-titration with 3 different doses of Kuvan. Treatments consisted of 3 consecutive 2-week courses of Kuvan at doses of 5, then 20, and then 10 mg/kg/day. Blood Phe level was monitored after 2 weeks of treatment at each dose level. Results: At baseline, mean (+/-SD) blood Phe was 844 (+/-398)

umol/L. At the end of treatment with 5, 10, and 20 mg/kg/day, mean (+/-SD) blood Phe levels were 744 (+/-384) umol/L, 640 (+/-382) umol/L, and 581 (+/-399) umol/L, respectively.

Study 4 -- A multicenter study of 90 children with PKU, ages 4 to 12 years, who were on Phe-restricted diets and who had blood Phe levels less than or equal to 480 umol/L at screening. All patients were treated with open-label Kuvan 20 mg/kg/day for 8 days. Response to Kuvan was defined as a greater than or equal to 30% decrease in blood Phe from baseline at Day 8. Results: At Day 8, 50 patients (56%) had a greater than or equal to 30% decrease in blood Phe.

BioMarin is also currently developing PEG-PAL (PEGylated recombinant phenylalanine ammonia lyase or 'PAL') an investigational enzyme substitution therapy for the treatment of PKU for patients who do not respond to Kuvan and/or for those who wish to reduce blood Phe levels beyond what is possible with Kuvan.

Expert Bio:

Barbara K. Burton, MD

Director, PKU Program
Professor of Pediatrics
Northwestern University's Feinberg School of Medicine

Dr. Barbara Burton is a Professor of Pediatrics at Northwestern University Medical School and a clinical geneticist at Children's Memorial Hospital. She graduated from Northwestern University Medical in 1973 and then completed her pediatric residency and fellowship in genetics at Children's Memorial Hospital. From 1978-1988, she was on the faculty of the Bowman Gray School of Medicine of Wake Forest University in Winston-Salem, North Carolina.

In 1989, Dr. Burton returned to Chicago to assume a position as Director of the Center for Medical Genetics at Michael Reese Hospital and professor and Head of the Division of Genetics at the University of Illinois College of Medicine. Her major clinical and research interests are in the areas of inborn errors of metabolism, connective tissue disorders, neurogenetic disorders and prenatal genetic screening and counseling. Dr. Burton has completed a presentation on Kuvan, Naglazyme and Aldurazyme at the 57th Annual Meeting of the American Society of Human Genetics.

Special interests: PKU and other metabolic disorders, lysosomal storage disorders, neurogenetic disorders, cardiomyopathy, Marfan syndrome

Previous/Current Studies:

Recommendations for evaluation of responsiveness to tetrahydrobiopterin (BH4) in phenylketonuria and its use in treatment

Safety and Tolerability Study of rAvPAL-PEG to Treat Phenylketonuria