Kuvan facts

Traditionally, in phenylketonuria (PKU), a lifelong low-phenylalanine (Phe) diet, supplemented with a phe-free protein substitute, has been the only treatment. Most children on diet treatment can only eat a very limited amount of natural protein. Daily protein allowance rarely exceeds more than 1 slice of ordinary bread per day – with the rest of the diet consisting of artificial foods. Not surprisingly, evidence suggests that many people have difficulty with complying with their diet. Poorly treated children with PKU have lower IQ and executive deficits (i.e. working memory, processing skills), low mood and anxiety, these complications frequently continue into adulthood. Recently, the European Guidelines (2017) recommended that everyone with PKU deserves consideration of BH4 (Kuvan) responsiveness and treatment.

How does Kuvan work?

An enzyme called phenylalanine hydroxylase (PAH) normally breaks down the amino acid phenylalanine into tyrosine. To help the enzyme work more efficiently, it is assisted by a chemical called BH4. In PKU, the PAH enzyme is defective leading to a buildup of Phe in the blood and brain. Kuvan is a drug treatment. It is a synthetic form of BH4. It stimulates the activity of residual PAH and helps restore enzyme action, thereby reducing blood phenylalanine levels.

Kuvan is used in combination with a low phenylalanine diet.

What advantages does it bring?

For patients with PKU who are responsive to Kuvan it will achieve the following:

- It lowers blood phenylalanine levels and will help improve and maintain acceptable blood phenylalanine control over time. This in turn will sustain cognitive function.
- It improves phenylalanine intake usually by at least 2 to 3-fold.
- As the phenylalanine (natural protein) allowance improves, the amount of protein substitute is correspondingly decreased.

A small percentage of patients with mild PKU may be able to stop dietary treatment with BH4.

Ultimately, the degree of diet relaxation with Kuvan will depend on blood phenylalanine control. It will vary from patient to patient.

Does Kuvan work for everyone with PKU?

- Approximately 20–30% of patients with mild or moderate PKU mutations. have been shown to respond to Kuvan. These patients typically carry mutations of phenylalanine hydroxylase that only partially reduce the activity of the enzyme, resulting in a milder/moderate form of the disorder.
- Up to 10% of patients with severe PKU may show a slow response.
- Kuvan helps both children and adults with PKU.

How much Kuvan do you give?

- The dose of Kuvan depends on body weight.
- The permitted dose range of Kuvan is 5-20 mg/kg/day, with a usual starting dose of 10 mg/kg.

How do you take Kuvan?

- The prescribed number of tablets are dissolved in water, drunk within 15 to 20 minutes and taken with a meal.
- Kuvan should be taken at the same time each day, usually at breakfast time.

How do you know Kuvan is working?

BH4-responsiveness should be determined on an individual case basis. The degree of responsiveness is characterised by the extent of improvement in blood phenylalanine levels and increase in natural protein intake.

An initial satisfactory response is defined as a reduction in blood phenylalanine levels of at least 30%, following a 24/48 hour loading test with Kuvan.
**Is Kuvan effective?**

Many studies have investigated the effectiveness of Kuvan. There is very good evidence to indicate that Kuvan is effective and that it enables people with PKU to eat significant amounts of ‘normal’ foods which has many nutritional and social benefits. Data also suggests that it improves blood phenylalanine control and maintains cognitive functioning. It has been studied in infants, children and adults. Kuvan has been routinely used in Europe for 9 years and the USA for 10 years and much long term European and USA efficacy data is accumulating.

**How long has this drug been available?**

The European Commission granted a Kuvan marketing licence which is valid throughout the European Union in December 2008. Initially Kuvan was approved for patients aged 4 years and over.

Recently, the efficacy and safety of Kuvan has been demonstrated in children <4 years of age which has led to its European approval in this age category since 2015.

So far, Kuvan has rarely been used in the UK. Commissioners for NHS England, Scotland and Wales have not agreed to fund Kuvan. However, Kuvan can be prescribed for PKU pregnancy.

**Is it available in other countries?**

- It is available in most countries throughout the world. Over 2000 patients with PKU worldwide are treated with Kuvan.
- It is used commonly in 23 other European countries e.g. Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, France, Germany, Hungary, Italy, Latvia, Lithuania, Luxembourg, Netherlands, Norway, Portugal, Romania, Russia, Slovakia, Slovenia, Spain, Switzerland and Turkey. In countries like Netherlands and Portugal it is offered to all patients with PKU.

**How do you know if you are a Kuvan responder?**

Kuvan loading tests determine which patients are BH4 responsive. There is no gold standard for performing this test, but it is usually conducted by a 24/48 hour loading test with Kuvan. Some countries give Kuvan daily for 4 weeks to establish its effectiveness.

**Is it possible to predict Kuvan responsiveness in any other way apart from a Kuvan loading test?**

In the UK, we do not perform routine mutation analysis in patients with PKU, but this information may be helpful in predicting Kuvan responsiveness in patients with either two null mutations (complete absence of enzyme activity – so an unlikely Kuvan responder) or with two BH4 (Kuvan) responsive mutations (a likely Kuvan responder).

**Are there any side effects of the drug?**

- Kuvan is a well-tolerated drug with a good safety profile. The most common side effects are:
  - Headache
  - Runny nose and nasal congestion
  - Sore throat
  - Diarrhoea
  - Vomiting
  - Cough

**Prescription of Kuvan**

- Treatment with Kuvan must be started and supervised by a doctor/dietitian who are experienced in treating PKU.
- It is important that patients continue with a diet low in phenylalanine and protein substitute when taking Kuvan.
- Intake of dietary phenylalanine (exchanges) and protein substitute must be monitored and adjusted according to blood phenylalanine levels.