



Canadian Expert Drug Advisory Committee Final Recommendation — Plain Language Version

SAPROPTERIN

(Kuvan — Biomarin Pharmaceutical [Canada] Inc.)

Indication: Phenylketonuria

Recommendation:

The Canadian Expert Drug Advisory Committee (CEDAC) recommends that Kuvan, which is also called sapropterin, not be listed by Canada's publicly funded drug plans for the treatment of phenylketonuria (PKU).

Reasons for the Recommendation:

1. There was not enough information to identify the type of individuals with PKU for whom Kuvan would provide enough improvement to be cost-effective.

Of Note:

The Committee believes that Kuvan can lower the phenylalanine (Phe) levels in the blood of some patients with PKU. However, the manufacturer did not give enough details on how to identify the type of patients that would get improvements that would be cost-effective. The proposed Kuvan Starter Program can identify patients whose blood Phe levels go down, as demonstrated in the medical studies, but it is not clear whether the patients whose Phe levels go down will also show important improvements in their health and well-being. Starting and stopping rules for Kuvan treatment that are based on important improvements in health and well-being are needed. It would be worthwhile for the manufacturer to work with the publicly funded drug plans to decide what improvements should occur in patients that would warrant paying for Kuvan. The rules developed should take into account the age of patients and the type of PKU.

Background:

Kuvan works by activating an enzyme in the body, called Phe hydroxylase, which is needed to break down Phe. Phe is an amino acid that is found in food. Phe hydroxylase does not work right or is not present in individuals with PKU, which leads to high levels of Phe in the blood. High levels of Phe in the blood are toxic to the brain and can lead to lower intelligence and a decrease in the ability to think clearly.

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Not all individuals with PKU will get lower blood Phe levels when treated with Kuvan. It is not possible to know whether or not Kuvan will result in lower Phe levels for an individual until he/she starts taking Kuvan. Health Canada recommends that individuals with PKU taking Kuvan also follow a low-Phe diet. The dose of Kuvan depends on the individual's weight. The recommended starting dose is 10 mg/kg per day, but the dosage may be adjusted within the range of 5 mg/kg to 20 mg/kg per day. Kuvan is available as 100 mg tablets that can be dissolved in water or apple juice.

Summary of CEDAC Considerations:

To make their decision, the Committee considered the following information prepared by the Common Drug Review (CDR): a review of the medical studies of Kuvan and a review of the economic information prepared by the manufacturer of Kuvan. Also, CEDAC considered information that patient groups submitted about outcomes and issues important to patients who have the condition for which the drug is indicated or who might use the drug.

Clinical Trials

CEDAC reviewed two studies conducted in individuals with PKU whose blood levels of Phe decreased by 30% or more when they tried Kuvan for eight days.

PKU-003

- Before the start of study PKU-003, 485 individuals with PKU, who were at least eight years old and who were not following their strict low-Phe diet closely, were given Kuvan at a dose of 10 mg/kg per day for eight days. After eight days of treatment, 96 (20%) of the individuals were able to get Phe levels that were at least 30% lower than before they started treatment. Individuals who had lower blood Phe levels before starting treatment were more likely to achieve a decrease of at least 30% than those with higher blood Phe levels. For example, 54% of individuals whose blood Phe level before treatment was less than 600 umol/L were able to achieve a decrease of at least 30%. However, only 18% of individuals with a blood Phe level of 600 umol/L to 1,200 umol/L before treatment achieved a decrease of at least 30% and only 10% of individuals with a blood Phe level of more than 1,200 umol/L achieved at least a 30% reduction. Individuals whose blood levels of Phe decreased by 30% or more were allowed to enter into PKU-003. Of the 96 individuals whose blood levels of Phe had decreased by 30% or more, 89 of them entered into PKU-003.
- PKU-003 was a six-week study that compared Kuvan 10 mg/kg per day with placebo (a tablet containing no active medication). Of the 89 individuals in the study, 87 (98%) finished the six weeks.

PKU-006

- PKU-006 was a two-part study with children, aged four to 12 years, with PKU, who were on a low-Phe diet and had an average Phe blood level of less than 480 umol/L. In part one of the study, children received Kuvan at a dose of 20 mg/kg per day for eight days. Those children whose blood Phe levels decreased by 30% or more and who had a blood Phe level of 300 umol/L or less were allowed to continue to part two of the study. Fifty (56%) of the 89 children treated with Kuvan 20 mg/kg per day for eight days in part one of the study had a decrease of 30% or more in their blood Phe levels, and 46 entered part two of PKU-006.

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- Part two of PKU-006 was a 10-week study that compared Kuvan 20 mg/kg per day with placebo. Forty-three (94%) of the 46 children that entered part two of PKU-006 finished the 10 weeks.

Outcomes

The main purpose in PKU-003 was to measure the change in blood Phe level at week six from when they entered into the study; the main purpose in PKU-006 was to measure the amount of dietary Phe supplement that the children could take at week 10 while keeping blood Phe levels at less than 360 umol/L.

Other measurements were defined in advance in the CDR systematic review protocol, and were discussed by the Committee, including quality of life, nutritional status, side effects, and serious side effects. Neither study looked at neuropsychological performance (e.g., level of intelligence or memory), quality of life, growth, or freedom regarding diet.

Information provided by the patient group focused on the costs and difficulties of staying with a strict low-Phe diet, and pointed out that a drug that decreases the need for a strict diet could reduce the burden of the disease and improve quality of life.

Results

Efficacy or Effectiveness

- In PKU-003, Kuvan-treated individuals with PKU had more lowering of blood Phe compared with placebo-treated individuals at six weeks; a 235.9 umol/L decrease versus a 2.9 umol/L increase respectively. Also, after six weeks, 54% of individuals taking Kuvan compared with 23% of individuals taking placebo, had Phe levels of 600 umol/L or less; 32% of individuals taking Kuvan compared with 2% of individuals taking placebo had blood Phe levels of 360 umol/L or less.
- In the part of PKU-006 that compared Kuvan with placebo, the average amount of dietary Phe supplement that could be added to the diet was 21 mg/kg per day for Kuvan compared with 2.9 mg/kg per day for placebo.

Harms (Safety and Tolerability)

- Approximately 600 individuals with PKU took Kuvan in PKU-003, PKU-006, and other studies. In about 80% of cases, the length of the treatment was approximately eight days. No individuals stopped taking part in the study due to side effects in the PKU-003 and PKU-006 studies.
- There were no serious side effects in PKU-003; in part two of PKU-006, two serious side effects were reported (streptococcal infection in the Kuvan group and appendicitis in the placebo group).
- Side effects were mostly mild; the most common side effects in Kuvan-treated individuals included, headache, upper respiratory tract infection (common cold), and cough.

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Cost and Cost-Effectiveness

The yearly cost of Kuvan depends on dose and patient weight. The yearly cost could range from \$24,090 for a 25 kg individual receiving 5 mg/kg per day to \$180,675 for a 75 kg patient at a dose of 20 mg/kg per day.

The Kuvan studies largely focused on changes in blood Phe levels. The lack of information on other outcomes related to improvements in health and well-being makes it difficult to determine the cost-effectiveness of Kuvan.

Patient Input Information

One patient group provided information regarding what is important to individuals with PKU.

- Low-Phe diets are complicated, do not taste good, and are expensive if the individual does not have coverage for low-protein foods.
- The most important thing for individuals with PKU is the ability to eat a more ordinary diet, while avoiding the problems caused by increased blood Phe levels.
- Freedom in terms of diet is expected to decrease the financial burden on individuals with PKU and improve their quality of life.

Other Discussion Points:

- The ability of Kuvan-treated children to take in more Phe supplement in study PKU-006 was not linked to medical impact or quality of life data.
- Based on the data available, it has not been proven that Kuvan at the higher 20 mg/kg daily dose is more useful than lower doses.
- Kuvan bioavailability (ability to be absorbed by the body and reach the tissues of the body) is greater when the complete tablet is swallowed, but in PKU-003 and PKU-006 the tablets were dissolved in water or juice. Absorption of Kuvan may also increase 30% to 80% when taken with a high-fat meal. Thus, the doses used in the studies may be larger than necessary to achieve the amount of blood Phe lowering seen in the studies.
- The Committee recognized that, given the low number of individuals with the disease condition, the usual cost-benefit considerations may not apply.

CEDAC Members Participating:

Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Dr. Doug Coyle, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, and Dr. Yvonne Shevchuk.

Regrets:

None

Conflicts of Interest:

None

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About this Document

The information contained within this plain language version of the Canadian Expert Drug Advisory Committee (CEDAC) Recommendation about this drug is based on the information found within the corresponding technical version of the CEDAC Recommendation.

In making its recommendation, CEDAC considered the best clinical and pharmacoeconomic evidence available, up to that time. Health care professionals and those requiring more detailed information are advised to refer to the technical version available in the [CDR Drug Database](http://www.cdr.ca) on the CADTH website (www.cadth.ca).

Background on CEDAC

CEDAC is a committee of the Canadian Agency for Drugs and Technologies in Health (CADTH). The committee is made up of drug evaluation experts and public members. CEDAC provides recommendations about whether or not drugs should be listed for coverage through the participating publicly funded drug plans; however, the individual drug plans make their own decision about whether or not to cover a drug.

In making its recommendations, CEDAC decides if the drug under review ought to be covered by the participating public drug plans based on an evidence-informed review of the medication's effectiveness and safety, and based on an assessment of its cost-effectiveness in comparison with other available treatments. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CEDAC deliberations.

The CEDAC Recommendation neither takes the place of a medical professional providing care to a particular patient, nor is it intended to replace professional advice. CADTH is not legally responsible for any damages arising from the use or misuse of any information contained in or implied by the contents of this document.

The statements, conclusions, and views expressed herein do not necessarily represent the views of Health Canada, the federal government, any provincial or territorial government, or any pharmaceutical manufacturer.

The manufacturer has reviewed this document and has not requested the deletion of any confidential information.

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