



Canadian Agency for
Drugs and Technologies
in Health

COMMON DRUG REVIEW

CEDAC FINAL RECOMMENDATION

SAPROPTERIN (Kuvan – Biomarin Pharmaceutical [Canada] Inc.) Indication: Phenylketonuria

Recommendation:

The Canadian Expert Drug Advisory Committee (CEDAC) recommends that sapropterin not be listed.

Reasons for the Recommendation:

1. Patient details were insufficient to identify a subpopulation for whom sapropterin may provide a significant clinical benefit that is cost-effective.

Of Note:

Although the Committee found sufficient evidence that sapropterin lowers blood phenylalanine (Phe) levels in certain patients with phenylketonuria (PKU), the submission did not provide sufficient details of how to identify the patients who would benefit in a cost-effective manner. The proposed Kuvan Starter Program is suitable only to screen patients to identify “responders,” but such a response in the clinical trials did not differentiate low response from clinically important response. Starting and stopping rules, beyond the screening stage, that are linked to substantive benefit are needed. It would be advisable for the manufacturer to work with provinces to establish these requirements with respect to age, PKU classification, and specific benefits to be achieved that support the price of this product.

Background:

Sapropterin is a synthetic form of tetrahydrobiopterin (BH4), the cofactor for Phe hydroxylase. It is approved by Health Canada in conjunction with a Phe-restricted diet to reduce blood Phe levels in patients with hyperphenylalaninemia due to BH4-responsive PKU. The recommended starting dose is 10 mg/kg per day. Once responsiveness has been established, the dosage may be adjusted within the range of 5 mg/kg to 20 mg/kg daily, based on response to therapy. It is available as 100 mg tablets.

Common Drug Review

CEDAC Meeting – November 17, 2010; CEDAC Reconsideration – January 19, 2011

Notice of CEDAC Final Recommendation – January 26, 2011

Page 1 of 4

© 2011 CADTH

Summary of CEDAC Considerations:

The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of randomized controlled trials (RCTs) of sapropterin, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Clinical Trials

The systematic review included two double-blind RCTs of patients with BH4-responsive PKU (PKU-003 and PKU-006). Patients eligible for both double-blind trials were those that had demonstrated a 30% or greater reduction in blood Phe levels following an eight-day challenge with sapropterin.

PKU-003

- A total of 485 children (≥ 8 years) and adults who were not adherent to a strict low-Phe diet (56% with a baseline Phe level greater than 900 $\mu\text{mol/L}$) were treated with sapropterin 10 mg/kg per day for eight days before enrolment in PKU-003, 96 (20%) demonstrated a 30% or greater reduction in blood Phe levels and were thus eligible to enter PKU-003. The proportion of patients who achieved the 30% or greater reduction in blood Phe varied based on baseline blood Phe level; $< 600 \mu\text{mol/L}$ (54%), 600 $\mu\text{mol/L}$ to 1,200 $\mu\text{mol/L}$ (18%), and $> 1,200 \mu\text{mol/L}$ (10%). Of the 96 patients achieving the 30% or greater reduction in blood Phe, 89 entered PKU-003.
- PKU-003 was a six-week double-blind RCT that compared sapropterin 10 mg/kg per day with placebo. Of the 89 patients randomized, 87 (98%) completed the six-week study.

PKU-006

- PKU-006 was a two-part study that enrolled children, four to 12 years old with PKU who were adherent to a Phe-restricted diet and had a mean blood Phe level of 480 $\mu\text{mol/L}$ or less, and an estimated Phe tolerance of $\leq 1,000$ mg per day. Patients who responded to an eight-day challenge of sapropterin 20 mg/kg per day in part one (defined as a 30% or greater reduction in blood Phe levels) and had a blood Phe level of 300 $\mu\text{mol/L}$ or less on day eight were enrolled in part two; part two of the study was a 10-week double-blind RCT that compared sapropterin 20 mg/kg per day with placebo.
- Of 89 low-Phe diet-adherent children treated with sapropterin 20 mg/kg per day for eight days in part one of PKU-006, 50 (56%) achieved a 30% or greater reduction in blood Phe, of whom 46 entered part two of PKU-006. Of the 46 patients randomized in part two, 43 (94%) completed the 10-week study.

Outcomes

The primary outcome in PKU-003 was the change in blood Phe level from baseline to week six, and the primary outcome in PKU-006 was the Phe supplement tolerated at week 10 while maintaining blood Phe levels of less than 360 $\mu\text{mol/L}$.

Other outcomes, defined a priori in the CDR systematic review protocol, discussed by the Committee, included quality of life, nutritional status, adverse events, and serious adverse events. Neither trial included validated measures of neuropsychological performance, quality of life, growth, or diet liberalization. Of note, patient input focused on the costs and difficulties of

adhering to a Phe-restricted diet and indicated that a drug that reduced the necessity for such strict dietary control could lessen the burden of the disease and improve quality of life.

Results

Efficacy or Effectiveness

- In PKU-003 sapropterin-treated patients experienced a statistically significantly greater mean reduction in blood Phe compared with placebo at six weeks; -235.9 $\mu\text{mol/L}$ versus $+2.9$ $\mu\text{mol/L}$ respectively. In addition, a statistically significantly greater proportion of sapropterin-treated patients, compared with placebo-treated patients, achieved blood Phe levels of 600 $\mu\text{mol/L}$ or less (54% versus 23%) and blood Phe levels of 360 $\mu\text{mol/L}$ or less (32% versus 2%) in PKU-003.
- In the double-blind RCT phase of PKU-006, the mean Phe supplement tolerated was 21 mg/kg per day for sapropterin compared with 2.9 mg/kg per day for placebo.

Harms (Safety and Tolerability)

- Approximately 600 patients were exposed to sapropterin in PKU-003, PKU-006, and related trials. In about 80% of cases, treatment duration was approximately eight days. There were no withdrawals due to adverse events during PKU-003 or PKU-006.
- There were no serious adverse events in PKU-003; in part two of PKU-006 two serious adverse events were reported (streptococcal infection in the sapropterin group and appendicitis in the placebo group).
- Adverse events were mostly mild; commonly observed adverse events in sapropterin-treated patients included, headache, upper respiratory tract infection, and cough.

Cost and Cost-Effectiveness

The annual cost of sapropterin is dependent on dose and patient weight. The cost could range from \$24,090 for a 25 kg individual receiving 5 mg/kg to \$180,675 for a 75 kg patient receiving a dose of 20 mg/kg.

Clinical data on sapropterin focused on blood Phe levels. The lack of clinical information for sapropterin complicates the examination of its cost-effectiveness.

Patient Input Information:

- One patient group provided information related to outcomes of importance to patients.
- Phe-restricted diets were described as complicated, unpalatable, and financially burdensome in the case of patients who do not have coverage for low-protein foods.
- The outcome of greatest importance to patients is the ability to eat a more ordinary diet while avoiding the adverse consequences of increased blood Phe levels.
- Liberalization of diet is expected to decrease the financial burden on patients and improve their quality of life.

Other Discussion Points:

- The increase in Phe tolerance observed in study PKU-006 was not linked to clinical impact or quality of life data.
- Based on available evidence, the advantage of using sapropterin at the higher 20 mg/kg per day dose is unproven.

Common Drug Review

Common Drug Review

- In one study, sapropterin bioavailability was greater with intact tablets, but in the included trials tablets were dissolved in water or juice. Absorption of sapropterin may also increase 30% to 80% when taken with a high-fat meal. Thus, the doses used in the trials may be larger than required to achieve the observed reductions in blood Phe levels.
- The Committee recognized that, given the low incidence of the disease condition, the usual cost-effectiveness 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

About this Document:

CEDAC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CEDAC made its recommendation. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CEDAC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The Final 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 view of Health Canada or any provincial, territorial, or federal government or the manufacturer.

Common Drug Review