CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

SAPROPTERIN – RESUBMISSION

(Kuvan — BioMarin Pharmaceuticals Canada Inc.)

Indication: To reduce blood phenylalanine levels in patients with hyperphenylalaninemia due to BH_4-responsive phenylketonuria

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that sapropterin, in conjunction with a phenylalanine (Phe)-restricted diet, be reimbursed to reduce blood Phe levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin (BH_4)-responsive phenylketonuria (PKU) with the following criteria and condition.

Clinical Criteria:
Demonstrated response to an initial 6-month trial of sapropterin and:

1. Compliance with low protein diet, formulas, and treatment with sapropterin.
2. Achievement of one or more of the following:
   2.1. Normal sustained blood Phe levels [less than 360 µmol/L] (at least 2 levels measured at least 1 month apart).
   2.2. Sustained blood Phe reduction of at least 30% (at least 2 levels measured at least 1 month apart) compared to baseline if the Phe baseline level is less than 1200 µmol/L.
   2.3. Sustained blood Phe reduction of at least 50% (at least 2 levels measured at least 1 month apart) compared to baseline if the Phe baseline level is greater than 1200 µmol/L.
3. Demonstrated increase of dietary protein tolerance based on targets set between the clinician and patient.
4. Managed by a physician specialized in metabolic/biochemical diseases.

Condition:
Price to be reduced by over 80%.

Reasons for the Recommendation:
1. The available evidence suggests that sapropterin treatment can reduce Phe levels in conjunction with a Phe-restricted diet and this treatment effect may be associated with increased tolerance of dietary Phe that may permit some degree of diet liberalization.
2. CDR reanalysis of the manufacturer's economic models suggested that sapropterin is associated with an incremental cost-utility ratio (ICUR) of over $500,000 per quality-adjusted

life-year (QALY) versus Phe-restricted diet alone and that a price reduction of at least 82% would be required for the ICUR to approach $100,000 per QALY.

Of Note:

1. The Committee noted that PKU is a rare condition for which there exists an unmet need in terms of pharmacological alternatives to a strict diet to maintain Phe levels within the recommended range.
2. Criteria required to define responsiveness to sapropterin treatment during the 6-month initial treatment period are in place within jurisdictions that reimburse sapropterin. Such criteria should be managed by individual jurisdictions.

Background:

Sapropterin has a Health Canada indication in conjunction with a Phe-restricted diet to reduce blood Phe levels in patients with HPA due to BH_4-responsive PKU.

Summary of CDEC Considerations:

CDEC considered the following new evidence available since the previous review by the CADTH Common Drug Review (CDR) of sapropterin: a systematic review of RCTs of sapropterin; a critique of the manufacturer's pharmacoeconomic evaluation; patient group-submitted information about outcomes and issues important to patients with PKU; and a supplemental review of the association between increased Phe tolerance and diet liberalization in HB_4-responsive PKU patients.

Patient Input

Patient input was provided by the Canadian PKU and Allied Disorders Inc. (CanPKU). The following issues were raised in the patient input received by CADTH:

- Families worry about the cost of sapropterin as, without coverage, it is unaffordable for most patients.
- In patients with sapropterin experience, sapropterin is seen as a positive, life-altering treatment that not only leads to a decrease and sometimes a stabilization in blood Phe levels but also allows the patient to eat a more normal diet and avoid or even reverse the many adverse consequences associated with higher blood Phe levels.
- Patients on sapropterin have reported beneficial cognitive impacts, improved academic performance, improved executive functioning and focus, improved energy, and increased confidence in their futures. In many cases, the thought of returning to the strict Phe-restricted diet should sapropterin be unattainable is devastating.
- Adverse events (AEs) noted by patients on sapropterin included heartburn, gastroesophageal reflux disease (GERD), acid reflux or stomach discomfort, sleep disturbances, hyperactivity, stomach pain, headache, nausea, diarrhea, agitation, nasal congestion, cough, vomiting, joint pain, and dizziness; however, these were reported to be mild and often disappeared over time.

Clinical Trials

Two phase 3 RCTs met the selection criteria for inclusion in the systematic review. PKU-016 (N = 206) was a double-blind, placebo-controlled, parallel-arm trial in patients aged eight years and older with PKU who were on a Phe-restricted diet. PKU-016 consisted of two 13-week treatment

periods: a double-blind randomized treatment period comparing sapropterin 20 mg/kg/day and placebo (both in conjunction with a Phe-restricted diet) and an open-label treatment period in which patients randomized to placebo in the first treatment period crossed over to open-label sapropterin, while maintaining a Phe-restricted diet. The SPARK study (n = 56) was an open-label, parallel-arm trial in patients younger than four years of age with PKU who were on a Phe-restricted diet and who had Phe blood levels within the target range (120 to 360 µmol/L). The SPARK study compared sapropterin 10 mg/kg/day plus a Phe-restricted diet to a Phe-restricted diet alone over 26 weeks.

Key limitations of the trials were the lack of a matched placebo in the SPARK study, the small patient numbers and relatively short duration of the trials, the lack of validation of measured outcomes or minimal clinically important differences (MCIDs) in patients with PKU, the lack of control for multiplicity in the statistical analyses, and the large placebo effect observed in both trials.

Outcomes

The following outcomes were defined a priori in the CDR systematic review protocol:

- Quality of life
- Health care resource utilization
- Change in Phe blood levels
- Neurophysiologic and neurocognitive effects
- Growth parameters
- Nutritional status
- Proportion of responders
- Change in Phe tolerance
- Mortality, AEs, serious adverse events (SAEs), and withdrawals due to adverse events (WDAEs).

There were two co-primary outcomes in PKU-016: the change from baseline to week 13 in the Attention Deficit Hyperactivity Disorder Rating Scale (ADHD-RS) or Adult ADHD Self-Report (ASRS) total score in Phe responders with ADHD symptoms and the proportion of patients with a Clinical Global Impression–Improvement (CGI-I) scale rating score of 1 (very much improved) or 2 (much improved) at week 13 in Phe responders with or without ADHD symptoms. The primary outcome in the SPARK trial was the change in dietary Phe tolerance from baseline at week 26.

Efficacy

In Study PKU-016, at week 13, Phe levels decreased by approximately 30% from baseline in the sapropterin + diet arm and remained largely unchanged in the placebo + diet arm. After week 13, Phe levels remained relatively stable in the sapropterin + diet arm, but decreased in the placebo + diet arm as these patients crossed over to receive open-label sapropterin + diet during the open-label treatment period. At week 26, mean Phe levels were similar between the two arms, although the Phe levels exceeded the upper limit of the Phe target range (360 µmol/L). No statistical comparisons of Phe levels were conducted between treatment arms in PKU-016. In the SPARK study, at week 26, the mean (standard error [SE]) change from baseline was –10.1 ([redacted]) µmol/L in the sapropterin + diet arm and 23.1 ([redacted]) µmol/L in the diet alone arm and the difference was not statistically significant. These findings imply that diet alone can maintain Phe blood levels in the target range.

Those patients who demonstrated a 20% reduction from baseline in Phe blood levels following treatment with sapropterin 20 mg/kg/day for up to one month were considered to be Phe responders. Of the 206 patients randomized in PKU-016, 118 patients (57.3%) were Phe responders. In the SPARK study, all patients entering the trial were required to be BH_4 responders. Although mean Phe blood levels were reduced from baseline in all treatment arms in both trials, the clinical significance of the magnitude of the reduction is unclear, as the MCID for Phe blood level reduction (i.e., Phe response) is unknown and the per cent reduction in Phe blood levels used to identify Phe responders (i.e., 20% or 30%) is arbitrary. In both trials, diet remained unchanged.

The primary outcome in the SPARK study was dietary Phe tolerance, which was defined as the prescribed amount of dietary Phe (mg/kg/day) tolerated while maintaining mean Phe blood levels within the target range of 120 to 360 µmol/L. Phe tolerance steadily increased in the sapropterin + diet arm as opposed to the diet alone arm over the course of the trial. At week 26, the mean (SE) Phe tolerance was 80.6 (4.2) mg/kg/day in the sapropterin + diet arm and 50.1 (4.3) mg/kg/day in the diet alone arm. The difference between treatment arms at week 26 (30.5 [95% confidence interval (CI), 18.7 to 42.3]) was statistically significant. These findings must be interpreted in the context that the SPARK study included only children aged four years and younger who were already in the target Phe blood level range of 120 to 360 µmol/L with dietary therapy alone. Although there was a statistically significant increase in dietary Phe tolerance with sapropterin + diet compared with diet alone in the SPARK study, this was not linked to improved quality of life. In addition, the long-term studies summarized in Appendix 6 of the Clinical Review Report, which were provided as new information by the manufacturer, also do not provide any evidence that improved Phe tolerance is linked to diet liberalization or improved quality of life. Evidence from a supplemental review of available literature describing BH_4-responsive patients suggested that the magnitude of the increase in Phe tolerance that is associated with sapropterin treatment can permit PKU patients to liberalize their diets through discontinuing Phe-free medical food supplements.

The effects of sapropterin treatment on neuropsychiatric and neurocognitive effects were investigated using various instruments in Study PKU-016, whereas in the SPARK study, only the effects of treatment on neuromotor developmental milestones were reported. In general, ADHD symptoms improved from baseline to week 13 in all treatment groups, but there were no differences between groups, with the exception of the Inattention subscale score. These results are also limited by the fact that the MCIDs have not been established for this instrument in patients with PKU and a correction factor was applied to the ASRS score, which has not been used previously in PKU or other disease areas. [redacted]

The included trials did not include any outcomes pertaining to quality of life, health care resource utilization, or nutritional status.

Harms

Most patients (> 75%) in both trials, regardless of treatment arm, experienced treatment-emergent AEs; however, the frequencies of AEs were similar between treatment arms and most were mild or moderate in severity. In PKU-016, the most frequent AEs were headache, nasopharyngitis, and vomiting, whereas in the SPARK study, they were pyrexia, cough, decreased amino acid level, and vomiting. There were no deaths in either trial, few patients with SAEs, and only one patient with a WDAE in PKU-016. The safety findings from the new clinical evidence are consistent with those in the original CDR review and support the view that sapropterin is generally safe and well tolerated. No new safety issues were identified.

Cost and Cost-Effectiveness

The manufacturer submitted a confidential price of $33.00 per 100 mg tablet of sapropterin. Based on representative body weight values obtained from trials of sapropterin, and depending upon dosage, annual costs for an 11 kg patient were estimated at $12,000 to $36,000; $24,000 to $72,000 for a 29 kg patient; and $48,000 to $169,000 for a 68 kg patient. The manufacturer submitted a cost-utility analysis comparing sapropterin plus Phe-restricted diet versus Phe-restricted diet alone in children and adults with PKU over a lifetime time horizon (110 years) from the perspective of a Canadian public payer. Two versions of the model were provided: in Model 1, the probability of adequate Phe-level control at six weeks was defined as blood Phe < 360 µmol/L; and in Model 2, control was defined as Phe reduction > 30%. These probabilities were obtained from a six-week randomized study comparing sapropterin with placebo (PKU-003). Some patients with adequate control at six weeks were assumed to achieve dietary Phe tolerance and could transition to a more liberal (i.e., a limited rather than strict) diet, based on the findings of the SPARK trial. Patients with inadequate control of blood Phe levels after six weeks were at risk of developing mild or severe neurocognitive disorders, based on a retrospective study of PKU outcomes conducted in Tunisia. Other inputs, such as costs and utility estimates, were obtained from published literature. Drug costs for sapropterin in the first year were halved as the manufacturer provides initial therapy (six months).

CDR noted the following key limitations of the analysis:

- The model assumes that six-week Phe level response determines lifetime Phe level response; however, this may not be the case, as there is uncertainty regarding the long-term durability of the effect of sapropterin.
- The model assumes that sapropterin modifies the probability of permanent neurocognitive damage, based on an observational study from a setting where screening for PKU was absent. However, studies more reflective of the Canadian setting have shown that early dietary treatment of PKU can eliminate the risk of severe cognitive impairment, and that normal health and educational attainment are possible. Hence, the manufacturer's model likely overestimated the risk and severity of adverse neurocognitive outcomes associated with inadequate Phe-level control, as well as the benefit (in terms of utility gain) of sapropterin.
- The model assumes the same effects of sapropterin for patients of all ages. However, the trials that inform the model enrolled specific age groups (eight years and older in PKU-003, and zero to four years in SPARK3). Therefore, it is unclear if the results of the cost-utility analysis are generalizable to the intended patient population.
- The model assumes that increased Phe tolerance observed in the SPARK trial translates to meaningful liberalization of diet and a consequent increase in utility. However, the relationship between Phe tolerance and diet liberalization is uncertain. Therefore, the degree of utility benefit associated with improved Phe tolerance, if any, is uncertain. As well, it was

assumed in the model that sapropterin-treated patients with Phe-level control had higher utility than diet-controlled patients, regardless of whether they experienced improved Phe tolerance. This was considered inappropriate because utility gains with sapropterin are likely to occur only if diet can be liberalized.
- The model may overestimate the clinical and resource consequences of neurocognitive disorders among patients with PKU. As well, costs related to neurocognitive disorders were from a French study, which may not be applicable to Canada.
- The submitted model does not align with the proposed reimbursement criteria for sapropterin. In particular, to qualify for treatment beyond six months, the criteria require either a demonstrated increase in dietary protein tolerance or clinically meaningful improvements in neurobehavioural or neurocognitive function; these conditions are not implemented in the model.
- Model 1 was considered more appropriate than Model 2, as the risk of neurocognitive disorders and the potential for diet liberalization are more likely to be associated with absolute Phe levels than percentage reductions from baseline.

CDR performed a reanalysis to address the identified limitations where possible. In particular, the risk of neurocognitive disorders among patients with inadequate Phe-level control was set to 0 (or alternatively, all such disorders were assumed to be of mild severity), utility gains could only occur among sapropterin-treated patients if they experienced improved Phe tolerance, and Canadian costs for neurocognitive disorders were applied. Based on Model 1 with a zero risk of neurocognitive outcomes, sapropterin was associated with an incremental cost-utility ratio (ICUR) of $573,314 per quality-adjusted life-year (QALY) versus Phe-restricted diet alone. If the risk of neurocognitive disorders (and the benefits of sapropterin) were maintained as per the manufacturer's base case, but all such events were assumed to be of mild severity, the ICUR was $488,182 per QALY.

Other Discussion Points:

The studies of sapropterin did not indicate a direct effect on improving QOL. The Committee discussed the difficulty in determining the effects of sapropterin on diet liberalization through the use of surrogate end points such as Phe levels and tests of dietary Phe tolerance. Despite the absence of direct evidence, the committee recognized an unmet need for PKU patients to have an alternative to a strict Phe-free diet. The committee accepted that evidence provided by a review of the relationship between Phe levels and diet liberalization, in conjunction with patient input, suggested that diet liberalization is likely associated with an improvement in QOL.

Research Gaps:

The Committee proposed that future research should be carried out to clearly demonstrate the efficacy of sapropterin with respect to liberalizing the diet of PKU patients and improving QoL using high-quality, appropriately designed RCTs.

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

Regrets:
July 20, 2016 Meeting: None
October 19, 2016 Meeting: None

Conflicts of Interest:
July 20, 2016 Meeting: None
October 19, 2016 Meeting: None

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