Common Drug Review
Pharmacoeconomic Review Report

September 2017

Drug	Sapropterin dihydrochloride (Kuvan)
Indication	In conjunction with a phenylalanine (Phe)-restricted diet to reduce blood Phe levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin-(BH4)-responsive phenylketonuria (PKU).
Listing Request	Ongoing funding of sapropterin (Kuvan) for non-pregnant patients and patients actively planning pregnancy who have a diagnosis of PKU and who have demonstrated a response to the initial 6 month trial of sapropterin and who meet ALL of the following criteria: 1. Compliance with low protein diet, formulas, and treatment with sapropterin; **AND** 2. Has achieved a) normal sustained blood Phe levels [Greater than 120 µmol/L and less than 360 µmol/L] (At least 2 levels measured at least 1 month apart); OR b) 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; OR c) 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; **AND** 3. Demonstrated increase of dietary protein tolerance based on targets set between the clinician and patient; **OR** 4. Clinically meaningful age-appropriate improvement in: a) neurobehavioural or neurocognitive function or impairment for patients with such impairments as determined by peer reviewed clinically validated scales; OR b) demonstrated improvement in Quality of Life using peer reviewed validated scales; AND Managed by a physician specialized in metabolic/biochemical diseases.
Dosage Form(s)	100 mg oral tablets
NOC Date	April 30, 2010
Manufacturer	BioMarin Pharmaceutical Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included two clinical experts in metabolic/biochemical diseases who provided input on the conduct of the review and the interpretation of findings.

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ABBREVIATIONS

AE	adverse event
CEA	cost-effectiveness analysis
CI	confidence interval
CUA	cost-utility analysis
FDA	Food and Drug Administration
HPA	Hyperphenylalaninemia
ICUR	incremental cost-utility ratio
ITT	intention-to-treat population
LY	life-year
MCADD	medium-chain acyl-coA dehydrogenase deficiency
Phe	Phenylalanine
PKU	Phenylketonuria
QALY	quality-adjusted life-year
SD	standard deviation
WDAE	withdrawal due to adverse event

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Sapropterin (Kuvan)
Study Question	"To assess, from a Canadian perspective, the economic impact of sapropterin in addition to standard care (Phe-restricted diet) compared to standard care alone in the treatment of PKU for children and adults patients."
Type of Economic Evaluation	CUA
Target Population	Children and adults patients with PKU
Treatment	In addition to Phe-restricted diet, 20 mg/kg/day SAP for a period of up to 1 month, and 5 to 20 mg/kg/day according to response to therapy once responsiveness established. Average daily dose is 10.5 tablets (100 mg/tablet).
Outcome(s)	QALYs Life-years
Comparator	Phe-restricted diet
Perspective	Canadian Ministry of Health
Time Horizon	Lifetime (110-year model horizon)
Results for Base Case	Model 1: Phe response defined by absolute level (< 360 µmol/L): ICUR = $274,862/QALY Model 2: Phe response defined by % reduction (> 30%) from baseline: ICUR = $308,664/QALY
Key Limitations	– Phe level response at 6 weeks with SAP or diet alone is extrapolated over a lifetime (110 years), based on trials of 6 to 26 weeks in duration. – The assumption that reduction in Phe levels with SAP will reduce risk of clinically significant permanent neurocognitive or neurobehavioural outcomes has not been confirmed. Risk of these outcomes was derived from a study reporting on a setting without universal screening for PKU; therefore, risk is likely overestimated in the model. – The disutility and cost of neurocognitive disorders are likely overestimated. – All patients achieving Phe level control with SAP were assumed to have a higher quality of life than patients achieving control with diet alone; however, patients are only likely to experience improved quality of life with diet liberalization (regardless of treatment strategy). – The relationship between Phe tolerance and diet liberalization is uncertain and diet liberalization has not been directly demonstrated in any of the available trials. Therefore, the degree of utility benefit associated with improved Phe tolerance, if any, is uncertain. – Model 2 may not appropriately reflect long-term treatment and outcomes of PKU, as neurological consequences are likely to be related to absolute Phe levels rather than relative reductions from baseline.
CDR Estimates	CDR performed the following key reanalyses to address identified limitations of the submitted model (Model 2 results are shown in parentheses): – Utility gain only with liberalized diet (regardless of treatment): ICUR = $353,050 per QALY ($412,613 per QALY). – Direct medical cost of learning disabilities from Canadian sources: ICUR = $295,257 per QALY ($327,932 per QALY).

	– All neurocognitive disorders assumed to be mild in severity: ICUR = $305,813 per QALY ($341,299 per QALY). If the risk of neurocognitive disorders is set to 0 for both treatment strategies: ICUR = $407,595 per QALY ($443,242 per QALY). According to the CDR base case incorporating Canadian medical costs, the same utility for patients on strict diet and a greater utility for patients on a more liberalized diet, and a zero risk of neurocognitive disorders, the ICUR was $573,314 per QALY ($658,501 per QALY in Model 2). If the risks for neurocognitive disorders used in the manufacturer's base-case analysis are retained (but all such disorders are assumed to be mild in severity), the resulting CDR base case ICUR was $488,182 per QALY ($573,314 per QALY in Model 2). Based on the more conservative assumption of a zero risk of neurocognitive disorders, a price reduction of 82% would be required for the ICUR to approach $100,000 per QALY and over 90% for the ICUR to approach $50,000 per QALY.

CDR = CADTH Common Drug Review; CUA = cost-utility analysis; ICUR = incremental cost-utility ratio; Phe = phenylalanine; PKU = phenylketonuria; QALY = quality-adjusted life-year; SAP = sapropterin.

EXECUTIVE SUMMARY

Background

Sapropterin (SAP) (Kuvan) is indicated in conjunction with a phenylalanine (Phe)-restricted diet to reduce blood Phe levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin (BH_4)-responsive phenylketonuria (PKU).[1] The initial dosage is 20 mg/kg/day administered orally for a period of up to 1 month. Once responsiveness to sapropterin (SAP) has been established, the dosage may be adjusted within the range of 5 to 20 mg/kg/day according to response to therapy. The confidential price per 100 mg tablet is $33.00.[2] Based on representative body weight values obtained from trials of SAP,[3-5] and depending upon dosage, annual costs for an 11 kg patient were estimated at $12,000 to $36,000; for a 29 kg patient, $24,000 to $72,000; and for a 68 kg patient, $48,000 to $169,000.

SAP was originally submitted to the CADTH Common Drug Review (CDR) in 2010, and in January 2011, the Canadian Expert Drug Advisory Committee (CEDAC) issued a Final Recommendation that Kuvan not be listed.[6] The key reason for the recommendation was that patient details were insufficient to identify a subpopulation for whom SAP may provide a significant clinical benefit that is cost-effective. A Request for Advice regarding SAP was submitted to CDR by CDR-participating drug plans in October 2011, which did not result in any changes to the recommendation.[7] The basis for the current resubmission is the availability of new clinical evidence. Following the 2011 CEDAC recommendation, provincial reimbursement of Kuvan has occurred in Ontario (as of February 2013) and Saskatchewan (as of September 2013).[8] The manufacturer states that reimbursement criteria in these provinces were developed with the understanding that new data would be forthcoming about the effectiveness and appropriate use of SAP to treat patients with PKU. The submitted price for SAP is the same as in the 2010 submission; however, a revised cost-effectiveness model was provided as part of the resubmission.

The manufacturer has proposed ongoing funding of SAP after a six-month initial trial if there is compliance with low-protein diet, formulas, and treatment with SAP and: 1) achievement of either normal sustained blood Phe levels (between 120 and 360 µmol/L) or sustained reduction of at least 30% from baseline (if baseline is less than 1,200 µmol/L) or 50% from baseline (if baseline is greater than 1,200 µmol/L); and 2) demonstrated increased tolerance of dietary protein, or clinically meaningful improvement in neurobehavioural and/or neurocognitive function or quality of life.

The manufacturer submitted a cost-utility analysis comparing SAP plus Phe-restricted diet versus a Phe-restricted diet alone in children and adult patients with PKU over a lifetime time horizon (110 years) from the perspective of a Canadian public payer.[2] 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% in Model 2. These probabilities were obtained from a six-week randomized study comparing SAP with placebo (PKU-003).[9] A proportion of patients with adequate control at six weeks was assumed to achieve dietary Phe tolerance and could transition to a more liberal "limited" (versus "strict") diet, based on the 26-week SPARK trial.[3] 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 conducted in Tunisia, a setting where neonatal screening for PKU did not occur.[10] Other inputs such as costs and utility estimates were obtained from published literature. Drug costs were obtained from the manufacturer, based on Canadian usage data, and drug costs in the first year were halved as the manufacturer provides the initial therapy (six months) under current provincial reimbursement criteria.

Summary of Identified Limitations and Key Results

- **Use of surrogate outcome and uncertainty regarding long-term outcomes**
  The manufacturer's 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 effect of SAP. The model also assumes that SAP modifies the probability of permanent neurocognitive damage, based on its effect on Phe levels. The risk and severity of neurocognitive disorders among patients with inadequate Phe level control were derived from an observational study in Tunisia where screening was absent. A number of European studies have shown that patients with PKU can have normal health and educational attainment upon early treatment with a Phe-restricted diet,[11-13] and a systematic review has shown that early dietary treatment of PKU can eliminate the risk of severe cognitive impairment.[14] Further, the PKU-016 trial demonstrated significant improvement in Phe levels with SAP, but attention-deficit/hyperactivity disorder (ADHD) outcomes were not consistently improved in the SAP group (see Clinical Review Report). Hence, the manufacturer's model likely overestimated the risk and severity of adverse neurocognitive outcomes associated with inadequate Phe level control, and the benefit of SAP in reducing the risk of such outcomes.
- **Consequences and costs of neurocognitive disorders**
  Neurocognitive disorders arising due to PKU are assumed to have similar consequences (i.e., utility values) as medium-chain acyl-coA dehydrogenase deficiency (MCADD). However, no justification was provided that MCADD and PKU are associated with similar outcomes. Observational studies from settings relevant to Canadian practice indicate that outcomes among patients with PKU are generally good, and quality of life is not impaired.[11-13] Further, neurocognitive impairment in PKU can be reversible with improved Phe level control, according to the clinical expert consulted by CDR, yet the manufacturer's model assumes irreversibility. Therefore, the model may overestimate the clinical and resource consequences of neurocognitive disorders among patients with PKU, which may underestimate the incremental cost-utility ratio (ICUR) for SAP. It is also noteworthy that the model incorporated costs related to neurocognitive disorders from a French study, which may not be applicable to Canada.[15]
- **Uncertainty in drug-controlled versus diet-controlled utility**
  The model assumes that utility will be higher for all patients taking SAP, regardless of whether they are able to liberalize their diet. In the available clinical trials, a proportion of patients achieved increased Phe tolerance in both treatment groups, with SAP-treated patients demonstrating higher dietary Phe tolerance than diet alone in the SPARK study.[3] However, the CDR clinical review found no direct evidence that SAP allowed for meaningful diet liberalization or improved quality of life. Nevertheless, the manufacturer applies the benefits of diet liberalization in terms of increased utility to all SAP-treated patients but does not apply the same benefit to diet-treated patients, potentially overestimating benefits in the former group compared with the latter, resulting in underestimation of the incremental cost per quality-adjusted life-year (QALY).
- **Uncertain relationship between Phe tolerance and diet liberalization**
  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 and diet liberalization has not been directly demonstrated in any of the available trials. Therefore, the degree of utility benefit associated with improved Phe tolerance, if any, is uncertain.
- **Different patient populations in trials compared with mode**
  The model assumes the same effects of SAP for patients at all ages (from birth to death). However, the two trials referenced in the model enrolled different age groups (ages eight years and older in

PKU-003,[9] and zero to four years in SPARK[3]). It is unclear whether the inputs from these studies are generalizable to the intended patient population. For example, the data on increased Phe tolerance were obtained from the SPARK study, which enrolled children up to the age of four years; therefore, their applicability to older children or adults is uncertain.

- **Transition from strict to limited diet**
  The manufacturer assumes "PKU not adequately controlled" and patients who developed neurocognitive disorders would switch to a limited diet. According to the clinical expert consulted by CDR, this is not likely to occur, as diet is the mainstay of treatment for PKU, particularly if Phe level control is suboptimal.
- **Lack of alignment between submitted model and proposed reimbursement criteria**
  The model submitted by the manufacturer does not align with the proposed reimbursement criteria for SAP. One of the proposed criteria for ongoing funding that is not operationalized in the model is the requirement for either a demonstrated increase in dietary protein tolerance or clinically meaningful improvements in neurobehavioural or neurocognitive function. These criteria suggest that SAP therapy could be discontinued for some patients even if they achieve the necessary Phe level response, potentially reducing overall costs in the SAP arm and improving its cost-effectiveness compared with the manufacturer's base-case result.

The manufacturer's base-case Model 1 results (control defined by Phe levels < 360 µmol/L) suggest SAP plus diet results in an additional 2.78 QALYs compared with diet alone at an additional cost of $763,868, driven primarily by drug acquisition costs ($126,473 per year); the resulting ICUR was $274,862 per QALY. According to Model 2 (control defined by Phe levels > 30%), the ICUR was slightly higher compared with Model 1. CDR considered Model 1 to be more appropriate, as the risk of neurocognitive disorders and potential for diet liberalization are more likely to be associated with absolute Phe levels than percentage reductions from baseline.

CADTH Common Drug Review Analyses

CDR performed the following key reanalyses of Model 1 to address some of the identified limitations. Reanalysis results for Model 2 are shown in parentheses.

1. **Utility assumptions for diet- and drug-controlled states:** If only patients who achieve a limited (versus strict) diet, regardless of treatment strategy, are assumed to have an improvement in utility (utility of 0.88 for limited diet; utility of 0.74 for strict diet), the ICUR increases to $353,050 per QALY for SAP compared with Phe-restricted diet ($412,613 per QALY in Model 2).
2. **Canadian cost of care:** When the direct medical cost of learning disabilities from Canadian sources is used ($2.24 versus $38.13 base case per day),[16] the ICUR rises to $295,257 per QALY ($327,932 per QALY in Model 2). Note that these data are not directly from patients with neurocognitive disorders.
3. **Exploration of uncertainty regarding risk and severity of neurocognitive disorders:** If all neurocognitive disorders are assumed to be mild in severity, the ICUR rises to $305,813 per QALY ($341,299 per QALY in Model 2). If the risk of neurocognitive disorders is set to 0 to reflect, as best as possible, the finding in the CDR clinical review of no significant differences in ADHD measures between SAP and diet alone, the ICUR increases to $407,595 per QALY ($443,242 per QALY in Model 2).
4. **Strict diet for "inadequately controlled" and those with neurocognitive disorders:** When strict instead of limited diet is assumed for "inadequately controlled" patients and those with neurocognitive disorders, the ICUR decreases slightly from the base case to $268,456 per QALY ($302,612 per QALY in Model 2).

The CDR base case was founded on a multi-way reanalysis incorporating the above changes to inputs and assumptions. Based on the CDR base case for Model 1 with an assumption of a 0 risk for neurocognitive disorders among patients with inadequate Phe level control, SAP was associated with an incremental cost of $806,283, 1.41 additional QALYs, and an ICUR of $573,314 per QALY ($658,501 per QALY in Model 2). If the risk of neurocognitive disorders is retained as per the manufacturer's model (but all such disorders are assumed to be mild in severity), the ICUR was $488,182 per QALY ($573,314 per QALY in Model 2).

Conclusions

CDR identified a number of limitations in the manufacturer-submitted model, the most important of which were unsupported assumptions regarding the long-term risk and severity of neurocognitive disorders among patients with PKU, and the impact of short-term Phe level response on risk. According to the CDR base case that attempted to address some of the main limitations of the model, the ICUR was between $488,000 and $573,000 per QALY gained (Model 1). Based on the latter (more conservative) ICUR value, a price reduction of 82% would be required for the ICUR to approach $100,000 per QALY and over 90% for the ICUR to approach $50,000 per QALY.

Significant uncertainty regarding the true cost-effectiveness of SAP remains, given the reliance of the model on the surrogate outcome of Phe levels, the absence of direct evidence that SAP benefits neurocognitive outcomes, diet liberalization or quality of life, and the very long time frame over which clinical benefits accrue. Under the most conservative scenario, in which SAP is considered to have no benefit on either neurocognitive outcomes or diet liberalization, SAP would be dominated by Phe-restricted diet alone as it would be associated with additional costs without any utility gains.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-utility analysis (CUA) comparing sapropterin (SAP) plus a phenylalanine (Phe)-restricted diet with a Phe-restricted diet alone in a cohort of patients with phenylketonuria (PKU).[2] The time horizon was patient lifetime (110 years), and the perspective was that of a Canadian public payer. A Markov model was developed in which all patients started in either the "PKU not adequately controlled" or the "PKU adequately controlled" health state, based on response after the first six weeks of treatment (Figure 1, Appendix 4: REVIEWER WORKSHEETS). Response at six weeks was defined based on the results of the pivotal randomized controlled trial (RCT) PKU-003. Two alternative approaches to defining response were modelled: Phe < 360 µmol/L (Model 1); and Phe reduction > 30% (Model 2).[2] The two models were identical except for the definition of response. Patients in the "PKU adequately controlled" state could achieve "dietary Phe tolerance" where patients switched from a strict diet to a (more liberal) limited diet; the proportions of "adequately controlled" patients who achieved Phe tolerance (and therefore transitioned to a limited diet) over time in the diet alone and SAP arms were obtained from the 26-week SPARK trial.[3] Patients in the "PKU not adequately controlled" state were at risk of developing "neurocognitive and neurobehavioural disorders" in each annual cycle. Probabilities of neurocognitive and neurobehavioural disorders were obtained from a retrospective study in Tunisia over 20 years, a setting where neonatal screening for PKU did not occur;[10] the proportion of neurocognitive disorders from this study was converted to an annual risk of 10% (of which 50% were assumed to be mild and 50% severe). All patients in either the "PKU not adequately controlled" or "neurocognitive disorders" states were assumed to switch from a strict diet to a limited diet. The model continued to run until all patients reached the absorbing state of death. Treatment discontinuation due to adverse events was not considered in the model.

Mortality rates by age were obtained from Statistics Canada life tables and assumed to be the same across treatments and health states. The proportion of male patients (0.58) was obtained from the PKU-003 trial and average patient weight ([redacted]kg) from data on file with the manufacturer. Patients entered the model from birth and responders were assumed to be on SAP for their lifetime.

PKU-related utility values were obtained from a manufacturer-sponsored study (reported in a conference abstract) in which time-trade-off and EuroQol 5-Dimensions Health-Related Quality of Life questionnaire (EQ-5D) valuations were performed on 100 adults and children.[17] Utility values were determined for three health states: blood Phe levels controlled by diet, controlled by drug, and uncontrolled. A full description of methods or exact utility values was not available from the abstract or other information submitted by the manufacturer. Utilities for neurocognitive and neurobehavioural disorders were taken from a published French cost-effectiveness analysis (CEA) of universal newborn screening for medium-chain acyl-coA dehydrogenase deficiency (MCADD).[15] Drug costs and average dosage per day (i.e., [redacted] SAP 100 mg tablets daily) were obtained from the manufacturer based on Canadian usage data. The drug costs in the first year were halved, as the manufacturer provides the initial therapy (six months) under current provincial reimbursement criteria. The unit cost for the Phe-restricted (i.e., strict) diet was taken from the Toronto Hospital for Sick Children, and the cost of the limited diet was assumed to be 50% that of the strict diet. Costs to manage cognitive disorders were also obtained from the French study,[15] and converted to

Canadian dollars. Ten GP visits and five specialist visits per year were assumed for patients regardless of health state. Both costs and effectiveness were discounted at 5%.

2. MANUFACTURER'S BASE CASE

In the base case for Model 1 (i.e., response at six weeks defined by Phe levels < 360 µmol/L), the manufacturer reported that SAP plus diet compared with diet alone was associated with an additional 2.78 QALYs and an incremental cost of $763,868, resulting in an incremental cost per QALY of $274,862.

In Model 2 (i.e., response at six weeks defined by Phe reduction > 30%), the manufacturer reported that SAP plus diet compared with diet alone was associated with an additional 3.43 QALYs and an incremental cost of $1,059,285, resulting in an incremental cost per QALY of $308,664.

TABLE 2: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE

	SAP + Diet	Diet Only	Difference
Model 1 (response at 6 weeks defined by Phe levels < 360 µmol/L)			
QALYs	11.65	8.87	2.78
Costs ($)	1,052,608 Drug + Diet: 884,493 Neuro:[a] 136,492 Other: 31,622	288,739 Diet: 60,408 Neuro: 196,709 Other: 31,622	763,868 Drug/Diet: 824,086 Neuro: –60,217 Other: 0
ICUR ($/QALY)			274,862
Model 2 (response at 6 weeks defined by reduction of Phe levels > 30%)			
QALYs	12.74	9.31	3.43
Costs ($)	1,337,700 Drug + Diet: 1,193,673 Neuro: 112,405 Other: 31,622	278,415 Diet: 64,134 Neuro: 182,659 Other: 31,622	1,059,285 Drug/Diet: 1,129,539 Neuro: –70,253 Other: 0
ICUR ($/QALY)			308,664

ICUR = incremental cost-utility ratio; neuro = neurocognitive disorders; Phe = phenylalanine; QALY = quality-adjusted life-year; SAP = sapropterin.

[a] Results were presented for a cohort of 100 patients in the manufacturer's submission.

2.1 Summary of Manufacturer's Sensitivity Analyses

Uncertainty was addressed using one-way deterministic sensitivity analyses performed on Model 1 (no sensitivity analysis was done on Model 2). Parameters tested included proportion of males (25% to 75%); probability of classic PKU neurocognitive disorders per year (0.05 to 0.15); cumulative lifetime proportion of "not adequately controlled" patients developing neurocognitive disorders (0.6375 to 0.87); discount rate (0% to 3%); daily number of SAP tablets (5 to 20); daily cost of strict diet ($12.01 to $20.01); daily cost of limited diet ($0 to $16.01); daily cost of cognitive disorders ($27.53 to $381.25); utility for the diet-controlled state (0.54 to 0.89); utility for the drug-controlled state (0.71 to 0.94); utility for the not adequately controlled state (0.2 to 0.73); utility for neurocognitive and neurobehavioural disorders (mild sequelae) (0.34 to 0.56), and utility for neurocognitive and neurobehavioural disorders (severe sequelae) (0.24 to 0.4).

The following parameters increased or decreased the incremental cost per QALY gained by more than 20% compared with the base-case result for Model 1:

- Number of SAP tablets per day ranged from 5 to 20 tablets (versus base case [redacted] tablets): cost per QALY $121,861 to 539,136
- Costs for neurocognitive disorders increased to $381.25 per day (versus $38.13 base case): cost per QALY $79,853
- Utility of drug-controlled patients decreased to 0.71 (versus 0.88 base case): cost per QALY $451,859
- Utility of "not adequately controlled" patients (for both groups) ranged from 0.20 to 0.73 (versus 0.56 base case): cost per QALY $154,564 to $445,966.

Probabilistic sensitivity analyses were not reported in the manufacturer's submission.

3. LIMITATIONS OF MANUFACTURER'S SUBMISSION

- **Use of surrogate outcome and uncertainty in modelling long-term outcomes**
  The CADTH Common Drug Review (CDR) considered Model 1 to be more appropriate than Model 2, as the risk of neurocognitive disorders and potential for diet liberalization are more likely to be associated with absolute Phe levels than percentage reductions from baseline.

  The manufacturer's model assumes that Phe level response at six weeks determines lifetime Phe level response; however, this may not be the case. Uncertainty remains regarding the long-term durability of response with SAP. As well, the clinical expert consulted by CDR indicated that the degree of Phe level control may change over the life course of patients with PKU (e.g., control may deteriorate as patients enter adolescence, due to poorer compliance with diet).

  The model assumes that SAP treatment modifies the probability of permanent neurocognitive damage caused by elevated blood Phe levels. The risk of neurocognitive disorders reported in an observational study from Tunisia, where screening for PKU was absent, is applied in the model to patients who do not achieve "adequate control" (as per the study and model definition). However, the consequences with respect to neurocognitive impairment are likely worse in an unscreened population compared with settings such as Canada with universal screening; even patients with PKU in Canada who do not achieve adequate Phe level control likely have better outcomes than patients who are unable to benefit from implementation of an early Phe-restricted diet due to lack of screening. Indeed, several European studies have shown that patients with PKU can have normal health and educational attainment with early treatment with Phe-restricted diet,[11-13] and a systematic review has shown that early treatment of PKU through diet can eliminate the risk of severe cognitive impairment[14] (see Appendix 6 for details). Further, the PKU-016 trial demonstrated significant improvement in Phe level with SAP (as well as with placebo); however, attention-deficit/hyperactivity (ADHD) measures were not consistently improved in the SAP group (i.e., no significant difference in Attention Deficit Hyperactivity Disorder Rating Scale (ADHD-RS)/ Adult Attention Deficit Hyperactivity Disorder Self-Report Scale (ASRS); the Inattention subscale significantly improved, but the minimal clinically important difference (MCID) is unknown). Hence, the manufacturer's model likely overestimated the risk and severity of adverse neurocognitive outcomes associated with inadequate Phe level control, and the benefit of SAP in reducing the risk of such outcomes. As such, it is plausible that the main benefit of SAP is improved Phe tolerance to an extent that allows some patients to move from a strict to a limited diet.

- **Consequences and costs of neurocognitive disorders**
  Neurocognitive disorders arising due to PKU are assumed to have similar consequences (i.e., utility values) to similar disorders associated with MCADD. However, there is no justification provided that MCADD and PKU have similar outcomes. Further, observational studies indicate that patients with PKU treated with diet generally have good outcomes; for the small number with poorer outcomes, the consequences are described to be quite mild (slightly lower IQ), and quality of life does not appear to be impaired.[11,12] Further, neurocognitive impairment may be reversible with improved Phe level control in some cases, according to the clinical expert consulted by CDR, yet the manufacturer's model assumes irreversibility. Therefore, the model may overestimate the clinical and resource consequences of neurocognitive disorders among patients with PKU. As well, the costs of neurocognitive disorders were obtained from a French study,[15] and it is uncertain whether these are applicable to the Canadian context.
- **Uncertainty in drug-controlled versus diet-controlled utility**
  The model assumes that utility will be higher for all patients taking SAP, regardless of whether they are able to liberalize their diet (i.e., move to limited versus strict). Based on input from the clinical expert consulted by CDR, quality of life for patients with controlled Phe levels may improve with SAP treatment if a less restrictive, more palatable diet can be implemented, due to increased tolerance of dietary Phe. In the available clinical trials, a proportion of patients achieved increased Phe tolerance in both treatment groups, with SAP-treated patients demonstrating higher dietary Phe tolerance than diet alone in the SPARK study.[3] However, the CDR clinical review found no direct evidence that SAP allowed for meaningful diet liberalization or improved quality of life. Nevertheless, the model applies the benefits of diet liberalization on utility to all SAP-treated patients and none of the diet-treated patients, potentially overestimating benefits in the former group compared with the latter, resulting in underestimation of the incremental cost per QALY.
- **Uncertain relationship between Phe tolerance and diet liberalization**
  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 and diet liberalization has not been directly demonstrated in any of the available trials. Therefore, the degree of utility benefit associated with improved Phe tolerance, if any, is uncertain.
- **Different patient populations in trials compared with model**
  The model assumes the same effects of SAP for patients at all ages (from birth to death). However, the two trials referenced in the model enrolled different age groups (ages eight years and older in PKU-003,[9] and zero to four years in SPARK[3]). It is unclear whether the inputs from these studies are generalizable to the intended patient population. For example, the data on increased Phe tolerance were obtained from the SPARK study, which enrolled children up to the age of four years, and it is uncertain whether these data can validly be applied to older children or adults.
- **Transition from strict to limited diet**
  The model assumes "PKU not adequately controlled" and patients who developed neurocognitive disorders would switch to a limited diet. According to the clinical expert consulted by CDR, this is not likely, as diet is the mainstay of treatment for PKU, particularly if control is suboptimal.
- **Error in utility calculation for neurocognitive disorders state**
  In the model, the disutility for the neurocognitive disorders state was subtracted from the utility for the "not adequately controlled" state (i.e., 0.56 – 0.11 = 0.45). However, the correct method is to multiply the utility values for the two states (i.e., 0.56 × 0.89 = 0.50).

- **Variability in jurisdictional coverage for Phe-restricted diets**
  As shown in Appendix 7: COVERAGE OF PHENYLKETONURIA FORMULAS AND MEDICAL FOODS ACROSS CANADA, reimbursement policies for Phe-restricted foods vary across Canada, with some offering unrestricted coverage for some products, others with annual or monthly caps, and still others with no coverage. For jurisdictions with no or limited coverage for Phe-restricted foods, there would be a lower cost offset associated with any benefits of SAP on diet liberalization; hence, the incremental cost per QALY would be slightly higher for these jurisdictions than suggested by the manufacturer's base case.
- **Lack of alignment between submitted model and proposed listing criteria:**
  The model submitted by the manufacturer does not align with the proposed listing criteria for SAP. One discrepancy relates to the proposed criteria for ongoing funding that patients comply with a low Phe, whereas the PKU-003 trial also included patients who were non-adherent to the Phe-restricted diet. Another element of the proposed criteria for ongoing funding that is not operationalized in the model is the requirement for either a demonstrated increase in dietary protein tolerance or clinically meaningful improvements in neurobehavioural or neurocognitive function. These criteria suggest that SAP therapy could be discontinued for some patients even if they achieve the necessary Phe level response, potentially reducing overall costs in the SAP arm and improving its cost-effectiveness compared with the manufacturer's base-case result.
- **Lack of probabilistic sensitivity analyses:**
  Uncertainty in the reported ICURs could not be fully assessed in the absence of probabilistic sensitivity analyses (PSAs).

3.1 CADTH Common Drug Review Analyses

CDR performed the following reanalyses of Model 1 to address some of the limitations identified above. The structure of the model did not permit implementation of the reimbursement criteria proposed by the manufacturer. Reanalysis results for Model 2 are shown in parentheses.

1. **Utility assumptions for diet- and drug-controlled states**
   If only patients who achieve a limited (versus strict) diet, regardless of treatment strategy, are assumed to have an improvement in utility (utility of 0.88 for limited diet; utility of 0.74 for strict diet), the ICUR is $353,050 per QALY ($412,613 per QALY in Model 2).
2. **Corrected error in calculating utility score for neurocognitive and neurobehavioural disorders**
   If the corrected utility estimates for patients with neurocognitive disorders are used (0.50 for mild and 0.43 for severe versus base case 0.45 and 0.32; see Appendix 4 for details), the ICUR rises to $316,790 per QALY ($352,776 per QALY in Model 2).
3. **Canadian cost of care**
   When the direct medical cost of learning disabilities from Canadian sources is used ($2.24 versus $38.13 base case per day),[16] the ICUR rises to $295,257 per QALY ($327,932 per QALY in Model 2). Note that these data are not directly from patients with neurocognitive disorders.
4. **Exploration of uncertainty regarding risk and severity of neurocognitive disorders**
   If all neurocognitive disorders are assumed to be mild in severity, the ICUR rises to $305,813 per QALY ($341,299 per QALY in Model 2). If the risk of neurocognitive disorders is set to 0 to reflect, as best as possible, the finding in the CDR clinical review of no significant differences in ADHD measures between SAP and diet alone, the ICUR increases to $407,595 per QALY ($443,242 per QALY in Model 2).
5. **Strict diet for "inadequately controlled" and those with neurocognitive disorders**
   When strict instead of limited diet is assumed for "inadequately controlled" patients and those with

neurocognitive disorders, the ICUR decreases slightly from the base case to $268,456 per QALY ($302,612 per QALY in Model 2).

6. **Exploration of uncertainty in response rate at six weeks**
   If the response rate for SAP is reduced by 50% (i.e., 22% adequately controlled) with no change to the response rate in the diet arm, the ICUR is $289,130 per QALY ($373,809 per QALY in Model 2). If the response rate is increased by 50% (i.e., 66%), the ICUR is $270,386 per QALY ($291,436 per QALY in Model 2). If the response rates from the PKU-016 trial (identified in the updated CDR clinical review of SAP) are used (i.e., 62.2% for SAP + diet versus 52.8% for diet alone based on Phe reduction > 20% from baseline) instead of the rates from the PKU-003 trial, the ICUR rises to $661,048 per QALY.

The CDR base case was based on a multi-way reanalysis incorporating: Canadian medical costs for learning disabilities ($2.24 per day); the same utility for patients on strict diet (0.74) and a higher utility for patients on a limited diet (0.88), regardless of treatment; an assumption of 0% risk of neurocognitive disorders (equal in both treatment groups); and an assumption that patients who are "not adequately controlled" or who have neurocognitive sequelae would not transition from a strict to a limited diet. Based on the CDR base case for Model 1, SAP was associated with an incremental cost of $806,283, 1.41 additional QALYs, and an ICUR of $573,314 per QALY ($658,501 per QALY in Model 2). Price reduction scenario analyses indicated that the price of SAP would have to be reduced by over 80% for the ICUR to approach $100,000 per QALY (82% price reduction yielded an ICUR of $100,006 per QALY), and over 90% for the ICUR to approach $50,000 per QALY (Table 3).

TABLE 3: PRICE REDUCTION SCENARIOS FOR CADTH COMMON DRUG REVIEW BASE-CASE ANALYSIS OF MODEL 1 (6-WEEK RESPONSE DEFINED BY PHE LEVELS < 360 MMOL/L)

ICURs for SAP Versus Standard of Care ($)		
Price	**Manufacturer's Base-Case Analysis**	**CDR Base-Case Analysis[a]**
Submitted	274,862	573,314
10% reduction	245,653	515,594
20% reduction	216,443	457,873
30% reduction	187,234	400,153
40% reduction	158,025	342,432
50% reduction	128,816	284,712
60% reduction	99,606	226,991
70% reduction	70,397	169,271
80% reduction	41,188	111,550
90% reduction	11,978	53,830

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; Phe = phenylalanine; SAP = sapropterin.
[a] Based on: no difference in the risk of neurocognitive disorders by treatment strategy, maintenance of a strict diet for all patients who do not achieve "adequate control" defined by Phe level, use of Canadian costs, and utility gain for adequately controlled patients who are able to achieve a less restricted diet.

TABLE 4: PRICE REDUCTION SCENARIOS FOR CADTH COMMON DRUG REVIEW BASE-CASE ANALYSIS OF MODEL 2 (6-WEEK RESPONSE DEFINED BY PHE REDUCTION > 30%)

ICURs for SAP Versus Standard of Care ($)		
Price	**Manufacturer's Base-Case Analysis**	**CDR Base-Case Analysis[a]**
Submitted	308,664	658,501
10% reduction	276,140	592,212
20% reduction	243,617	525,923
30% reduction	211,093	459,633
40% reduction	178,569	393,344
50% reduction	146,045	327,055
60% reduction	113,522	260,766
70% reduction	80,998	194,476
80% reduction	48,474	128,187
90% reduction	15,950	61,898

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; Phe = phenylalanine; SAP = sapropterin.
[a] Based on: no difference in the risk of neurocognitive disorders by treatment strategy, maintenance of a strict diet for all patients who do not achieve "adequate control" defined by Phe level, use of Canadian costs, and utility gain for adequately controlled patients who are able to achieve a less restricted diet.

Given the uncertainty regarding the risk of neurocognitive disorders, a sensitivity analysis was performed for the CDR base case in which the risks for neurocognitive disorders used in the manufacturer's base-case analysis are retained, but assuming that all such disorders would be mild in severity (Appendix 4: REVIEWER WORKSHEETS). The resulting ICUR was $488,182 per QALY ($573,314 per QALY in Model 2).

3.2 Patient Input

Patient group input received by CDR for this submission indicates that PKU places a considerable burden on patients and caregivers. Various degrees of neurocognitive and neuropsychiatric symptoms are described, such as difficulties in concentration, impaired memory, ADHD, shaking, and depression. These can lead to behavioural and social problems. Maintaining a Phe-restricted diet is described as "laborious, complex," and the diet itself as "unpalatable." The considerable time required to plan and prepare the diet takes away from other activities such as work and social events. Dietary restrictions can also lead to social isolation, and prevent travel. Parents of children with PKU describe considerable stress related to ensuring that their children adhere to the diet. Financial difficulties due to the high cost of Phe-restricted medical foods are also described.

The economic model submitted by the manufacturer addresses most of the issues identified by patients. In the model, control of Phe levels with SAP is assumed to be associated with better quality of life (i.e., a higher utility) than control with diet. Based on the patient group input, this assumption may be appropriate for patients who experience a significant improvement in Phe tolerance and are able to liberalize their diet. Indeed, the clinical trial evidence indicates that SAP responders have improved Phe tolerance, and some of the anecdotal experience reflected in the patient group input suggests that some patients are able to consume a normal diet on SAP. However, considerable uncertainty remains regarding the extent to which quality of life is better among patients achieving control of Phe levels with SAP versus those achieving control with diet alone, as the clinical trials of SAP did not assess this outcome directly.

4. CONCLUSIONS

CDR identified a number of limitations in the manufacturer-submitted model, the most important of which were unsupported assumptions regarding the long-term risk and severity of neurocognitive disorders among patients with PKU, and the impact of short-term Phe level response on risk. According to the CDR base case that attempted to address some of the main limitations of the model, the ICUR was between $488,000 and $573,000 per QALY gained (Model 1). Based on the latter (more conservative) ICUR value, a price reduction of 82% would be required for the ICUR to approach $100,000 per QALY and over 90% for the ICUR to approach $50,000 per QALY.

Significant uncertainty regarding the true cost-effectiveness of SAP remains, given the reliance of the model on the surrogate outcome of Phe levels, the absence of direct evidence that SAP benefits neurocognitive outcomes, diet liberalization or quality of life, and the very long time frame over which clinical benefits accrue. Under the most conservative scenario in which SAP is considered to have no benefit on either neurocognitive outcomes or diet liberalization, SAP would be dominated by Phe-restricted diet alone, as it would be associated with additional costs without any utility gains.

APPENDIX 1: COST COMPARISON

The cost comparison table for sapropterin (SAP) reflects the dosage range recommended in the product monograph (5 to 20 mg/kg/day).[1] Representative values for body weight were obtained from the trials included in the original and updated CADTH Common Drug Review (CDR) clinical reviews, and the manufacturer's economic model. Based on input from the clinical expert consulted by CDR, there are no other drugs currently indicated for this condition.

TABLE 5: COST COMPARISON TABLE FOR PHENYLKETONURIA TREATMENTS

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Daily Drug Cost ($)[b]	Average Annual Drug Cost ($)
Sapropterin dihydrochloride	100 mg	Tablet	33.0000[a]	5 to 20 mg/kg/day	11 kg: $33.00 to 99.00[c] 29 kg: $66.00 to 198.00[d] [redacted] kg: $99.00 to 396.00[e] 68 kg: $132.00 to 462.00[f]	$12,045 to 36,135 $24,090 to 72,270 $36,135 to 144,540 $48,180 to 168,630

PKU = phenylketonuria; SAP = sapropterin.
[a] Manufacturer-submitted price is the current market price for SAP.
[b] Based on number of 100 mg tablets required (rounded up to the nearest whole tablet).
[c] Assuming an average weight for patients aged 0 to 4 years based on the SPARK study.[3]
[d] Assuming an average weight for patients aged 4 to 12 years based on study PKU-006.[4]
[e] Mean body weight assumed in economic model submitted by manufacturer.
[f] Assuming an average weight for patients aged ≥ 8 years based on study PKU-016.[5] Mean body weight for adult patients (≥ 18 years of age) was not reported.

APPENDIX 2: SUMMARY OF KEY OUTCOMES

WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS SAP RELATIVE TO THE STANDARD OF CARE?

SAP Versus Standard of Care	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	Model 1: Phe levels (< 360 µmol/L), $274,862 per QALY Model 2: Reduction of Phe levels (>30%), $308,664 per QALY					

CE = cost-effectiveness; NA = not applicable; Phe = phenylketonuria; QALY = quality-adjusted life-year; SAP = sapropterin.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 6: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?			X
Comments *Reviewer to provide comments if checking "no"*	Numerous assumptions made in the model were not justified or fully clarified in the report.		
Was the material included (content) sufficient?		X	
Comments *Reviewer to provide comments if checking "poor"*	None		
Was the submission well organized and was information easy to locate?			X
Comments *Reviewer to provide comments if checking "poor"*	Numerous assumptions made in the model were not justified or fully clarified in the report.		

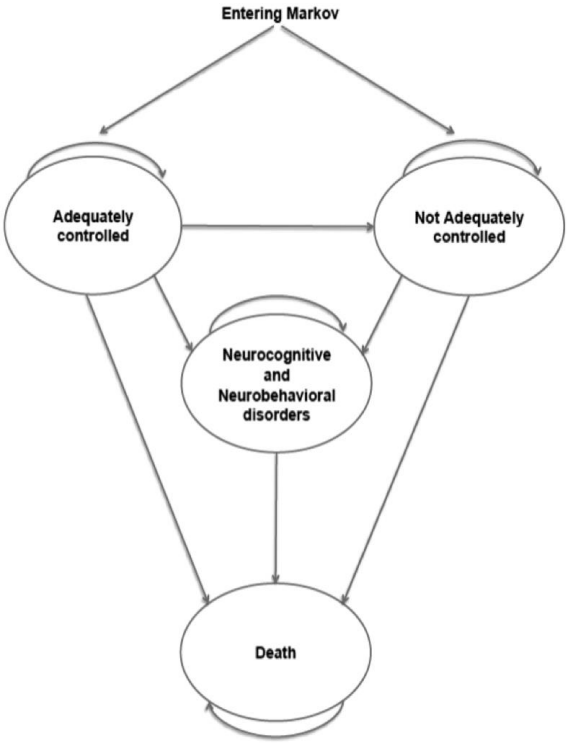
TABLE 7: AUTHOR INFORMATION

Authors	Affiliations		
Jean Lachaine, Valerie Piche-Richard	PeriPharm Inc.		
	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis	X		

APPENDIX 4: REVIEWER WORKSHEETS

1. Manufacturer's Model Structure

FIGURE 1: MANUFACTURER-SUBMITTED MODEL



Note: Not all modelled health states are shown in the figure (i.e., "adequately controlled" state with phenylalanine tolerance is not shown). In addition, "adequately controlled" patients are shown in the figure as being at risk for transition to neurocognitive and neurobehavioural disorders; however, this was not the case in the model.
Source: Manufacturer's Pharmacoeconomic Submission[2]

TABLE 8: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy — Phe levels and dietary Phe tolerance	In the PKU-003 trial, the proportion of patients "adequately controlled" (responders), based on Phe < 360 µmol/L (Model 1), was 32% for SAP + diet vs. 2% for diet alone; based on Phe reduction > 30% (Model 2), the proportions were 44% for SAP + diet vs. 9% for diet alone. Long-term Phe tolerance (enabling switch from strict to limited diet) was obtained from the SPARK study.	Reasonable. However, this is a surrogate (see below) and short-term trial outcomes are extrapolated over a lifetime. The PKU-003 trial also excluded patients younger than 8 years. The SPARK study included only patients from ages 0 to 4 years, with strict control of their Phe level (< 360 µmol/L). It is not clear if this applies to other age categories or Phe level 360 µmol/L.
Efficacy — diet	Phe levels (PKU-003) or % reduction inform the proportion of patients who transition from a strict to a limited diet (SPARK).	Reasonable. However, the trial time frame is short and long-term association is extrapolated.
Efficacy — neurocognitive disorders	Phe levels or % reduction inform the proportion of patients who develop mild or severe neurocognitive disorders.	While there is an association based on observational data, there is no evidence that SAP modifies risk of this outcome from trial data.

Data Input	Description of Data Source	Comment
Natural history	The probabilities of neurocognitive and neurobehavioural disorders were estimated from an observational study in Tunisia.	Not appropriate, as these data are unlikely to be transferable to Canada. There is no PKU screening in Tunisia; delayed identification is likely to substantially increase the probability and severity of neurocognitive disorders.
Natural history	Half of neurocognitive disorders are severe.	Not appropriate. Long-term observational studies indicate that in diet-treated patients, consequences are mild, if present at all (i.e., slightly lower IQ, etc.).[11,12]
Natural history	All patients who are "not adequately controlled" and patients with neurocognitive or neurobehavioural disorders are assumed to be treated with a limited (instead of strict) diet.	Not appropriate. Dietary management is the mainstay of treatment, particularly for patients in these health states.
Utilities — treatment	Utilities by treatment obtained from a manufacturer-sponsored conference abstract. Utility is 0.74 for diet-treated PKU and 0.88 for drug + diet-treated PKU, irrespective of whether diet can be liberalized. However, full text, methods, and exact values are not available from the abstract or manufacturer-submitted information.	Not appropriate. Utility is unlikely to be improved just by taking medication, unless there is a therapeutic effect. Phe tolerance likely improves for some patients treated with SAP; hence, utility may be higher for those who can switch to limited diet (regardless of treatment strategy), but there are no direct data to support this.
Utilities — neurocognitive disorders	Utility for mild and severe neurocognitive disorders obtained from patients with MCADD[a] — 0.45 and 0.32, respectively.	Not appropriate. Long-term observational studies indicate that in diet-treated patients with PKU, consequences are mild if present at all (i.e., slightly lower IQ, etc.),[11,12] and there is no decrement in quality of life.[11] There are no supporting data provided to justify that MCADD and PKU consequences are similar. Further, the adjusted utility is miscalculated in the model.
AEs (indicate which specific AEs were considered in the model)	Direct discontinuation due to AEs was not considered in the model.	Reasonable, as AEs are minor, as shown in the Clinical Review Report.
Mortality	Mortality rates by age were obtained from Statistics Canada life tables and assumed to be the same across treatments and health states.	Reasonable.
Costs		
Drug	Cost per day from manufacturer. Manufacturer also covered first 6-month drug cost under current reimbursement criteria.	Appropriate.
Diet	Obtained from the Toronto Hospital for Sick Children.	Appropriate.
Health state	Direct medical costs for cognitive disorders were obtained from a published CEA from France on MCADD.	Not appropriate. Uncertainty regarding transferability of European costs to Canadian setting.[11,12]

AE = adverse event; CEA = cost-effectiveness analysis; MCADD = medium-chain acyl-coA dehydrogenase deficiency; Phe = phenylalanine; PKU = phenylketonuria; SAP = sapropterin; vs. = versus.

[a] MCADD is a disorder of metabolism where episodes of relative fasting where patients develop hypoketotic hypoglycemia and liver dysfunction. Severe episodes may result in seizures or coma, and permanent brain damage depending on the severity of the event and number of episodes.

TABLE 9: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Treatment effect is assumed to remain constant over the 110-year model horizon.	Uncertain.
Treatment with sapropterin reduces risk of mild and severe neurocognitive disorders.	Uncertain. Such effects of sapropterin are extrapolated based on correlations between blood phenylalanine levels and neurocognitive and/or neuropsychiatric outcomes.
Probability of developing neurocognitive disorders among Canadian phenylketonuria patients is the same as in an observational study from Tunisia (where no screening occurs).	Not appropriate. Studies in settings more representative of Canada indicate that the risk of neurocognitive disorders, particularly severe disorders, among patients with phenylketonuria is likely small.

2. Manufacturer's Results

All relevant manufacturer base-case and sensitivity analysis results are presented in the main body of the report.

3. CADTH Common Drug Review Reanalysis

Given the uncertainty regarding the risk of neurocognitive disorders, a sensitivity analysis was performed for the CDR base-case analysis in which the risks for neurocognitive sequelae were included as per the manufacturer's base-case analysis, with an assumption that all such sequelae would be mild in severity. The utility for neurocognitive disorders was also corrected as described in the CDR univariate reanalyses (0.50 versus manufacturer's base-case value 0.45). In this analysis, SAP was associated with an incremental cost of $802,745, 1.65 additional QALYs, and an ICUR of $488,182 per QALY ($563,178 per QALY in Model 2).

TABLE 10: PRICE REDUCTION SCENARIOS FOR SENSITIVITY ANALYSIS OF CADTH COMMON DRUG REVIEW BASE CASE, MODEL 1 (6-WEEK RESPONSE DEFINED BY PHE LEVELS < 360 MMOL/L)

ICURs for SAP Versus Standard of Care ($)		
Price	**Manufacturer's Base-Case Analysis**	**CDR Base-Case Analysis[a]**
Submitted	274,862	488,182
10% reduction	245,653	438,816
20% reduction	216,443	389,450
30% reduction	187,234	340,084
40% reduction	158,025	290,718
50% reduction	128,816	241,352
60% reduction	99,606	191,985
70% reduction	70,397	142,619
80% reduction	41,188	93,253
90% reduction	11,978	43,887

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; Phe = phenylalanine; SAP = sapropterin.
[a] Based on: Canadian medical costs ($2.24 per day), the same utility for patients on strict diet (0.74) regardless of treatment with a greater utility for patients on a limited diet (0.88) regardless of treatment; an assumption that 100% of neurocognitive sequelae would be mild in severity; corrected utility value for neurocognitive disorders; and an assumption that patients who are "not adequately controlled" or who have neurocognitive sequelae would not transition from a strict to a limited diet.

TABLE 11: PRICE REDUCTION SCENARIOS FOR SENSITIVITY ANALYSIS OF CADTH COMMON DRUG REVIEW BASE CASE, MODEL 2 (6-WEEK RESPONSE DEFINED BY PHE REDUCTION > 30%)

ICURs for SAP Versus Standard of Care ($)		
Price	**Manufacturer's Base-Case Analysis**	**CDR Base-Case Analysis[a]**
Submitted	308,664	563,178
10% reduction	276,140	506,273
20% reduction	243,617	449,367
30% reduction	211,093	392,462
40% reduction	178,569	335,557
50% reduction	146,045	278,652
60% reduction	113,522	221,747
70% reduction	80,998	164,841
80% reduction	48,474	107,936
90% reduction	15,950	51,031

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; Phe = phenylalanine; SAP = sapropterin.
[a] Based on: Canadian medical costs ($2.24 per day), the same utility for patients on strict diet (0.74) regardless of treatment with a greater utility for patients on a limited diet (0.88) regardless of treatment; an assumption that 100% of neurocognitive sequelae would be mild in severity; corrected utility value for neurocognitive disorders; and an assumption that patients who are "not adequately controlled" or who have neurocognitive sequelae would not transition from a strict to a limited diet.

APPENDIX 5: SUMMARY OF OTHER COST-EFFECTIVENESS ANALYSES

A 2013 cost-effectiveness analysis (CEA) published as a conference abstract comparing sapropterin (SAP) with a phenylalanine (Phe)-free diet in patients with phenylketonuria (PKU) was identified (Elsisi et al.[18]). Table 12 summarizes the similarities and differences between the manufacturer-submitted model and the Elsisi study.

TABLE 12: COMPARISON BETWEEN ELSISI ET AL. AND MANUFACTURER-SUBMITTED MODEL

	Elsisi et al.[18]	Manufacturer
Comparators	SAP vs. Phe-free diet	SAP + diet vs. diet alone
Model	Markov model with annual cycle, with 6 health states (healthy, mild PKU, controlled mild PKU, classical PKU, controlled classical PKU, and death)	Markov model with annual cycle, with 5 health states (controlled, controlled with Phe tolerance, uncontrolled, neurocognitive disorders, and death).
Discount rate	3.5%	5%
Setting	Egypt	Canada
Model length (years)	10	110
Efficacy	Published studies in Egyptian patients with PKU and international published sources.	PKU-003 and SPARK trials
Mortality	NA	Canadian life table
Drug cost	NA	$33 per 100 mg tablet
Direct medical costs	Ministry of Health mandatory tariff in Egypt	Costs obtained from CEA on MCADD (Hamers 2012) and converted to Canadian dollars
QALY	International published sources (details not available)	Obtained from manufacturer-sponsored study on PKU (YHEC 2009), and CEA on MCADD (Hamers 2012)
Results	EGP £602,933/QALY (2013 $) (CAN $87,968/QALY)	CAN $274,862/QALY to $308,664/QALY (2014 $)

CAN = Canadian; CDR = CADTH Common Drug Review; CEA = cost-effectiveness analysis; EGP = Egyptian; ICUR = incremental cost-utility ratio; MCADD = medium-chain acyl-coA dehydrogenase deficiency; NA = not applicable; Phe = phenylalanine; PKU = phenylketonuria; QALY = quality-adjusted life-year; SAP = sapropterin; vs. = versus.

APPENDIX 6: SUMMARY OF LONG-TERM PHENYLKETONURIA STUDIES

Table 13 summarizes long-term studies in phenylketonuria patients identified by the CADTH Common Drug Review to validate assumptions in the manufacturer-submitted analysis.

TABLE 13: LONG-TERM STUDIES IN PATIENTS WITH PHENYLKETONURIA

Study	Origin	Patients	Method	Results
Smith 1978[13]	UK	47 (21 early vs. 26 late treated)	IQ	Fall in mean IQ of about 6 points after diet was withdrawn. Reversibility not assessed.
Schwartz 1988[12]	Switzerland	20 (0.1 to 15.6)	DQ/IQ test	Only 1 patient with IQ 75 to 85 and attended special school; others were in normal range.
Brumm 2004[19]	USA	24 (All except 1 on Phe diet until age 6; one patient stopped at age 5)	– Attention – Executive functioning – Learning and memory – Language functioning – Visual-perceptual skills – Emotional adjustment – Psychomotor speed and fine motor coordination	Average IQ with 1 borderline; visual-perceptual intact but compromised in copying complex figure. Fine motor coordination, psychomotor speed, and reaction time intact. Verbal skills within expected range but deficits in expressive naming and verbal fluency. Emotional functioning normal except 2 with moderate/severe depression and anxiety. Below average: Focused and sustained attention, mental flexibility, verbal learning, short- and long-delay recall. Language functioning improved with lower Phe levels.
Bosch 2007[11]	Holland	32 (18 to 30)	Course of Life questionnaire, RAND-36, cognitive scale	Normal health and educational attainment. More special education.
Enns 2010[14]	USA	Systematic review of 150 studies	1) Neurocognitive/ psychosocial 2) QoL 3) Brain pathology 4) Growth/nutrition 5) Bone pathology 6) Maternal PKU	1) Early diet eliminated severe cognitive impairment but overall intellectual functioning suboptimal (IQ in normal range but lower than general population); attentional problems; social and emotional difficulties; 2) mostly not different from reference values but suboptimal in positive emotions; lower Phe associated with better QoL; 4) slow growth in height and head circumference, excessive weight gain.

Study	Origin	Patients	Method	Results
Daelman 2014[20]	France	5 – poorly controlled; most stopped diet; mean Phe 1,633 µmol/L	Case study	No psychiatric symptoms; 75% mental retardation. Reintroduction can reverse some symptoms (50%).

DQ = developmental quotient; Phe = phenylalanine; PKU = phenylketonuria; QoL = quality of life; vs. = versus.

APPENDIX 7: COVERAGE OF PHENYLKETONURIA FORMULAS AND MEDICAL FOODS ACROSS CANADA

TABLE 14: COVERAGE OF PHENYLKETONURIA FORMULAS AND MEDICAL FOODS ACROSS CANADA

Province	Children		Adults	
	Formulas	Low-Protein Foods	Formulas	Low-Protein Foods
British Columbia	✓	✓$3,000 per patient per year	✓	✓$3,000 per patient per year
Alberta	✓	✓	✓	✓
Saskatchewan	✓	✓	✓	✓
Manitoba	✓	✓Up to $120/month age 0 to 12; up to $250/month age 13 to 18 years	✓	✓
Ontario	✓	✓	✓	✓
Quebec	✓	✓Up to $1,500 per patient per year	✓	✓Up to $1,500 per patient per year
New Brunswick	✓	✓Only staples (bread mix, flour, pasta)	✓	✓Only staples (bread mix, flour, pasta)
Nova Scotia	✓	✓Only staples (baking mix, pasta, cracker toasts, rusks)	✓	✓Only staples (baking mix, pasta, cracker toasts, rusks)
Prince Edward Island	✓	✓$3,600 per patient annually	✓	✓$3,600 per patient annually
Newfoundland and Labrador	✓Only 2 formulas	✓Only staples (pasta, bread mix, pizza shells, cheese)		

Source: Canadian PKU and Allied Disorders (April 2016).[21]

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