

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Pegvaliase (Palynziq)

Indication: For the treatment of patients with phenylketonuria (PKU) aged 16 years and older who have inadequate blood phenylalanine control (blood phenylalanine levels greater than 600 µmol/L) on existing management.

Sponsor: BioMarin Pharmaceutical (Canada) Inc.

Recommendation: Reimburse with Conditions

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Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that pegvaliase be reimbursed for the treatment of patients with phenylketonuria (PKU) aged 16 years and older who have inadequate blood phenylalanine control (blood phenylalanine levels greater than 600 µmol/L) despite dietary management only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One double-blind, randomized discontinuation trial (PRISM-2 RDT; N = 95) comparing pegvaliase with matching placebo in patients with PKU aged 16-70 years demonstrated that treatment with either 20 mg/day or 40 mg/day of pegvaliase (pooled active group) resulted in statistically significant and clinically meaningful improvement in blood phenylalanine (Phe) concentration after 8 weeks. The least squares mean (LSM) change in blood Phe levels from the RDT entry to Week 8 was 26.5 µmol/L (95% CI -68.3 to 121.3) in the pooled active group, versus 949.8 µmol/L (95% CI 760.4 to 1139.1) in the 20 mg/day placebo group, and 664.8 µmol/L (95% CI 465.5 to 864.1) in the 40 mg/day placebo group. There were statistically significant differences in LSM change from baseline between the pooled active group and each of the 20 mg/day placebo (-923.25 µmol/L; 95% CI -1135.04 to -711.46; P<0.0001) and 40 mg/day placebo (-638.27 µmol/L; 95% CI -858.97 to -417.57; P<0.0001) groups.

CDEC acknowledged that there was a need for additional effective treatment options for patients with PKU. Patients identified an unmet need for treatments that allow them to eat normally, and improve mental health and quality of life outcomes. No differences in inattention or mood symptoms were observed between the pegvaliase and placebo groups in PRISM-2 RDT; however, CDEC agreed with the clinical experts consulted by CADTH that differences in neurocognitive and neuropsychiatric function were unlikely to be detectable over the 8 week period of PRISM-2 RDT, given the high variability in the symptoms of adult patients with established PKU. Other outcomes important to patients, including health-related quality of life (HRQoL) and protein tolerance were not assessed in the trial.

The cost-effectiveness of pegvaliase is highly uncertain due to an absence of robust comparative evidence and the inappropriateness of the model structure. As such, a base case cost-effectiveness estimate was unable to be determined in patients with PKU who are 16 years or older who have inadequate blood Phe control despite dietary management. The committee considered exploratory analyses conducted by CADTH which determined the ICER was likely closer to \$1,923,797 per QALY when compared to medical nutritional therapy (MNT) alone, therefore pegvaliase is not cost-effective at a \$50,000 per QALY willingness to pay (WTP) threshold. A price reduction of at least 99% would be required for pegvaliase to achieve an ICER of \$50,000 per QALY.

Table 1. Reimbursement Conditions and Reasons

Reimbursement Condition	Reason	Implementation Guidance
Initiation		
1. Treatment with pegvaliase should be initiated in patients with PKU aged 16 years and older.	Evidence from PRISM-2 RDT demonstrated that pegvaliase resulted in a statistically significant improvement in blood Phe concentration in patients aged 16 to 70 years. The CADTH review identified no evidence to support the efficacy and safety of pegvaliase in patients younger than 16 years of age.	—
Renewal		
2. Patients should be assessed for treatment response using blood Phe concentration 8 -16 weeks after initiation of the treatment, and annually thereafter.	In the PRISM-2 RDT, the efficacy of pegvaliase was measured 8 weeks after the RDT entry.	Clinical experts suggested that the patients who undergo treatment with pegvaliase should be reviewed annually (by reviewing blood Phe levels obtained on a monthly schedule and by an annual review of protein tolerance); however, the evaluation of treatment response should be performed in a shorter interval after initiation of treatment as patients will need to adjust their diets based on Phe levels. Clinical experts considered a 16-week period to be sufficient for the establishment of treatment response.
3. Pegvaliase may be renewed for patients who demonstrate response to an initial 16-week administration of pegvaliase and achieve the following: <ul style="list-style-type: none"> 3.1. compliance with treatment with pegvaliase; and 3.2. sustained blood Phe levels of less than 600 µmol/L (at least 2 levels measured at least 1 month apart). 	The CADTH review did not identify any evidence that patients who do not exhibit these clinical criteria would benefit from further treatment with pegvaliase.	—
Discontinuation		
4. Pegvaliase should be discontinued upon the occurrence of a recurrent mild to moderate anaphylactic reaction	This condition reflects the discontinuation criteria from PRISM-2 RDT and safety considerations listed in the Product Monograph. The CADTH review did not identify any evidence to demonstrate the safety and potential benefits of continuing pegvaliase in patients with this condition.	—
Prescribing		
5. Pegvaliase should only be prescribed and monitored by	This condition is to ensure that treatment is prescribed only for appropriate patients	The initial doses of pegvaliase should be supervised and delivered in specialized

Reimbursement Condition	Reason	Implementation Guidance
clinicians with expertise in treating genetic and metabolic disorders.	and severe adverse effects are managed in an optimized and timely manner.	centers that are equipped to manage acute systemic hypersensitivity reactions. An epinephrine injection device should be prescribed for patients undergoing pegvaliase treatment.
Pricing		
6. A reduction in price	The cost-effectiveness of pegvaliase is highly uncertain. CADTH undertook a price reduction analysis based on an adjustment of health state utilities to be more in line with other chronic health conditions, increased syringe use in maintenance years, and lowered MNT adherence with pegvaliase and sapropterin. This analysis indicated that a 99% reduction in price is required to achieve an ICER of \$50,000 per QALY.	—

ICER = incremental cost-effectiveness ratio; MNT = medical nutritional therapy; Phe = phenylalanine; PKU = phenylketonuria; QALY = quality adjusted life years; RDT = randomized discontinuation trial; $\mu\text{mol/L}$ = micromoles per litre

Discussion Points

- Clinical experts noted that MNT can prevent severe neuropsychological complications if the treatment is established immediately after the diagnosis of PKU in infancy. However, CDEC agreed with the clinical experts that MNT may have partial and variable effectiveness in most adolescent and adult patients with PKU because adherence by these patients to medical nutrition is extremely challenging. CDEC recognized an unmet need for this patient population to have an additional effective treatment option.
- Patients expressed a need for treatment options that could improve control over blood Phe levels, improve natural protein intake and neurocognitive function, reduce PKU symptoms, decrease the burden of long-term disease and treatment-related consequences, and improve HRQoL. CDEC noted that no differences in inattention or mood symptoms were observed between the pegvaliase and placebo groups in PRISM-2 RDT; however, the committee acknowledged that the trial assessment period (8 weeks) was of insufficient duration to observe changes in neurocognitive and neuropsychiatric function. Other outcomes important to patients, including HRQoL and protein tolerance were not assessed in PRISM-2 RDT.
- CDEC noted that pegvaliase may allow some patients to liberalize their restricted diet while maintaining therapeutic levels of plasma Phe.
- While recognizing that PRISM-2 RDT was enriched with patients who were more tolerant to pegvaliase, CDEC acknowledged that the study findings could be generalized to the PKU population in Canada. CDEC discussed that adherence to pegvaliase would be a critical issue in the clinical practice, and acknowledged that outside of a trial setting, where there are less frequent follow up visits and clinical support, compliance with pegvaliase would likely be lower than that observed in the clinical trial.
- CDEC discussed the safety profile of pegvaliase and noted that this drug is associated with a risk of anaphylaxis. CDEC agreed with clinical experts that, overall, the adverse event rates reported in the pivotal trial could be underestimated, as the PRISM-2 study participants took mandatory premedication during re-introduction of study drug in the RDT phase, had more frequent clinical evaluations, and received additional training on the detection and management of adverse events compared with the general population of adult PKU population. However, the clinical experts believed that these factors would not be major impediments to generalizing the safety profile of pegvaliase from the PRISM-2 study to real world clinical practice.

Background

Phenylketonuria (PKU) is a monogenic autosomal recessive disorder and one of the most common inborn errors of metabolism. Patients with PKU have mutations in both alleles of the *PAH* gene encoding phenylalanine hydroxylase (PAH), an enzyme that catalyzes the conversion of phenylalanine (Phe) to tyrosine using tetrahydrobiopterin as a cofactor. PAH deficiency leads to uncontrolled blood Phe, which then crosses the blood-brain-barrier where it has neurotoxic effects. In adolescents and adults, uncontrolled Phe levels are associated with behavioural and psychiatric problems (inattentiveness and mood dysfunction, often collectively referred to as 'executive dysfunction'). PKU symptoms, in conjunction with treatments, negatively impact patient health-related quality of life (HRQoL) of patients via difficulties with employment, social relationships, and mental health.

PKU is rare, with an incidence of approximately 1:12,000 to 1:15,000 live births in Canada (equivalent to approximately 300 new cases per year). According to the sponsor, there are approximately 3,133 PKU patients living in Canada at present, of whom approximately [REDACTED] are being managed and approximately [REDACTED] are aged ≥ 16 years and currently being treated with sapropterin. The current cornerstone of PKU treatment is lifelong dietary control of Phe intake to curb blood Phe levels. This is principally accomplished by providing Phe-free foods and metabolic formulas with a small amount of "complete" Phe-containing protein allowed on top, sometimes collectively referred to as medical nutritional therapy (MNT). Adherence of adult patients with PKU to MNT is extremely challenging because low protein medical food is very unpleasant to taste and smell. Other than dietary restriction, the only other approved medication is sapropterin, a cofactor of the deficient PAH enzyme in PKU. Approximately 25% of patients with milder PKU have a biochemically detectable response to sapropterin.

Pegvaliase has been approved by Health Canada to reduce blood phenylalanine concentrations in patients with phenylketonuria (PKU) aged 16 years and older who have inadequate blood phenylalanine control (blood phenylalanine levels greater than 600 micromol/L) despite dietary management. Pegvaliase is a recombinant enzyme substitution therapy. It is available as prefilled syringes (2.5 mg/0.5 ml [5 mg/ml], 10 mg/0.5 ml [20 mg/ml], 20 mg/ml) and as recommended in the product monograph, dosing by self-administered daily subcutaneous injection should be titrated to a maintenance dose required to achieve blood Phe level ≤ 600 $\mu\text{mol/L}$, with a maximum dose of 60 mg daily.

Sources of Information Used by the Committee

To make their recommendation, the Committee considered the following information:

- A review of 1 phase III, four-part, four-arm, double blind, placebo-controlled, randomized discontinuation trial (RDT) with an extension period of OL treatment (PRISM-2); 1 phase III, OL, randomized, multicenter study (PRISM-1); 1 exploratory phase III substudy (PRISM-3); and 1 observational retrospective cohort study in adolescent and/or adult PKU patients.
- Patients' perspectives gathered by one patient group, Canadian PKU and Allied Disorders (CanPKU)
- Input from public drug plans and cancer agencies that participate in the CADTH review process
- Two clinical specialist with expertise diagnosing and treating pediatric and adult patients with PKU who have inadequate Phe control
- Input from one clinician group (three physicians specialized in treating metabolic disorders who care for adult patients with PKU in Canada).
- A review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups who responded to CADTH's call for patient input and from the clinical experts consulted by CADTH for the purpose of this review.

Patient Input

One submission, from the Canadian PKU and Allied Disorders (CanPKU), was received for this review. Between 30 November and 25 December 2021, CanPKU conducted online surveys (n=68 PKU patients, n=46 Canadian and n=14 US) and telephone interviews (n=5 patients experienced with pegvaliase, n=1 Canadian and n=4 US). Respondents narrated how PKU symptoms and the PKU protein-restricted diet had impacted their physical and mental health, employment, and social relationships. Almost all respondents ($\geq 95\%$) had experience with low-protein medical foods and formulas, 65% had experience with Kuvan, while only 21% had experience with pegvaliase. Respondents described barriers to existing therapies including poor taste, lack of satiety, inconvenient preparation and administration, high cost, and limited availability.

The vast majority ($\geq 85\%$) of respondents identified Phe control, reducing PKU symptoms, limiting long-term disease consequences, improving neurocognitive function, managing diet, reducing burden of treatment, improving HRQoL, and increasing natural protein intake as key outcomes of interest. Respondents experienced with pegvaliase reported that the drug limited long-term disease consequences, controlled Phe levels, reduced PKU symptoms, and had tolerable side effects such as injection site reactions, joint pain, and skin reactions.

Clinician Input

Input from Clinical Experts Consulted by CADTH

Two clinical specialists with expertise in the diagnosis and management of pediatric and adult patients with PKU who have inadequate Phe control provided input for this review. The clinical experts relayed that currently available therapies (MNT with or without sapropterin) can in theory successfully meet treatment goals by decreasing Phe and preventing the neuropsychological complications of PKU. However, because adherence to MNT is generally low, MNT is not effective in most patients and only a minor population of patients with milder PKU will respond to sapropterin. Pegvaliase would be used as last line treatment following MNT and, if appropriate, sapropterin. Pegvaliase may shift the treatment paradigm for some adult patients with PKU by allowing liberalization of diet while maintaining Phe control.

There were differences of opinion between the two clinical experts consulted by CADTH for this review regarding the subset of PKU patients who would benefit most from pegvaliase. One clinical expert felt that patients with high and uncontrolled Phe are most in need of an intervention to improve metabolic control that will lead to a decrease in their Phe levels and improved Phe tolerance. The clinical expert could not rule out the possibility that patients who are poorly compliant with MNT could become more compliant to therapies (including pegvaliase) over time as Phe levels decrease and focus improves. A second clinical expert felt that PKU patients who are highly compliant with MNT and other therapy and have the most severe forms of PKU would be the most suitable for treatment with pegvaliase. These patients are generally able to achieve Phe levels within the control range but have the most unpalatable diets and experience large deviations in Phe levels. These patients can be identified by assessing compliance with MNT and other therapy (assessed via mean Phe values) and PKU severity (assessed by PAH genotyping, variability in Phe levels, and/or by degree of restriction of complete protein intake). This clinical expert indicated that patients who are non-compliant with therapy would be the least suitable for treatment with pegvaliase.

The clinical experts relayed that complete protein tolerance (or Phe tolerance) and blood Phe levels are the most convenient tests to assess response to treatment and are most often used in clinical trials. Clinically meaningful responses to treatment would be reflected by, in order of importance, increased complete protein tolerance (or Phe tolerance) and protein intake to levels in the general population, improvement in HRQoL, and improvement in psychological metrics (neurocognitive performance, mood, attention, and working memory). According to the clinical experts, high blood Phe levels can be used to show that pegvaliase treatment is ineffective, and in patients with low Phe who liberalize their diets to include natural foods, stability of Phe levels with the treatment range can demonstrate improvements in protein tolerance. Patients who cannot maintain good Phe levels (or whose levels are not monitored) with MNT and pegvaliase are non-compliant and should be discontinued from treatment, as should patients who experience significant adverse reactions.

Clinician Group Input

A group of three physicians who care for adult patients with PKU in Canada provided input for this review. Although the clinician group echoed the challenges in adhering to the PKU diet and the limited proportion of patients who can benefit from sapropterin, views contrasting those of the clinical experts consulted by CADTH were presented on: (i) the connection between blood Phe levels and neurological symptoms, diet liberalization, and associated impacts on HRQoL in adult PKU patients, which the clinician group felt were tightly and reversibly linked; (ii) the importance of Phe control as a treatment goal and marker of treatment response in and of itself; (iii) the patient subset most suitable for pegvaliase treatment, which the clinician group felt was patients non-compliant with dietary restriction who cannot benefit from sapropterin and thus have poor or no Phe control; (iv) the patient subset least suitable for pegvaliase treatment, which the clinician group felt was patients able to maintain Phe levels within target range on MNT with or without sapropterin; and (v) the risks of very low Phe levels (e.g., <30 µmol/L) resulting from overtreatment with pegvaliase in patients who do not comply with Phe monitoring, which the clinician group felt were a potential concern. According to the clinician group, pegvaliase would be offered as last line treatment to adult PKU patients who have elevated Phe levels and neuropsychiatric symptoms and are able to self-administer the injection.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for pegvaliase. The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2. Responses to Questions from the Drug Programs

Implementation Issues	Clinical Experts' Response
Relevant Comparators	
<p>A comparator was not included in the submitted trials; the sponsor stated that placebo was the appropriate comparator citing the reason that a significant proportion of patients do not respond to sapropterin (e.g., challenges with long-term adherence to Phe-restricted diet, PAH deficiency).</p> <p>There is a retrospective comparison of long-term treatment effectiveness of pegvaliase versus sapropterin + diet and diet alone (Zori et al.) - not a head-to-head study. It compared the effectiveness of long-term pegvaliase treatment to standard care (i.e., sapropterin + diet or diet alone) among adults with PKU 18 years and older with blood Phe levels >600 µmol/L. Normalization of blood Phe levels (defined as ≤120 µmol/L) was achieved in 45% of patients receiving pegvaliase and none of those receiving sapropterin + diet. After 2 years of follow-up, 68% of patients on pegvaliase versus 20% of those on sapropterin + diet, achieved EU guideline-recommended Phe levels of ≤600 µmol/L; 65% of patients on pegvaliase versus 8% on sapropterin + diet achieved US guideline-recommended level of 360 µmol/L. There are limitations associated with this study including non-randomized patient populations and confounding baseline factors.</p> <p>What is the appropriate comparator for pegvaliase (sapropterin + diet versus placebo)?</p>	<p>According to the clinical experts, the appropriate comparator for pegvaliase is dietary restriction. Clinical experts noted that all patients with PKU are prescribed dietary restriction or medical food (although many are not compliant).</p>
<p>Sapropterin is the only medication available in Canada for the treatment of PKU in conjunction with a Phe-restricted diet. Access to sapropterin is restricted, in some jurisdictions, through special authorization (e.g., NB), limited use (e.g.,</p>	<p>CDEC acknowledged the drug plans' input and agreed that, where available, the use of sapropterin would be restricted to patients with biopterin-responsive PKU.</p>

Implementation Issues	Clinical Experts' Response
<p>NIHB) or through exceptional access/drug status program (e.g., ON, SK). Sapropterin was reviewed by CDEC (Oct 2016) and received a positive recommendation (BH4-responsive PKU). Not all jurisdictions may have sapropterin listed which would be a consideration if existing management is sapropterin + diet.</p>	
Considerations for Initiation of Therapy	
<p>Newborn screening for PKU is standard in Canada; diagnosed infants are immediately started on treatment to prevent long-term neurological damage. Blood Phe is controlled over the life course to reduce the risk of serious outcomes associated with PKU.</p> <p>Initiation criteria for sapropterin (CDEC recommendation) in aforementioned jurisdictions, in general, state that baseline blood Phe levels should be $>360 \mu\text{mol/L}$ despite compliance with low protein diet (require at least two levels during 3-to-6-month time frame).</p>	<p>The clinical experts consulted by CADTH noted that no patient, in otherwise good health, can be adherent to a properly designed Phe-restricted diet and have Phe levels $\geq 600 \mu\text{mol/L}$ for 6 months. This is physiologically impossible and Phe levels of all patients with PKU can theoretically be controlled with a proper diet. A compliant patient on diet with or without sapropterin would have Phe levels $< 600 \mu\text{mol/L}$; those that have higher Phe levels are usually non-compliant. Nevertheless, most adult patients with PKU will not be able to meet treatment goals and attain Phe levels $< 600 \mu\text{mol/L}$ due to limited compliance.</p>
<p>In the PRISM-1 study (phase III, multicenter, open label study that randomized pegvaliase-naïve patients to receive one of two regimens of pegvaliase), patients with a blood Phe concentration of $600 \mu\text{mol/L}$ or higher for at least 6 months prior to the study were eligible.</p>	<p>According to the clinical experts Phe monitoring is typically done monthly for adults. An average of values (at least four) over a 6-month period would be required to get realistic vision of Phe control. Single Phe values are too variable.</p>
<p>Given the sponsor's reimbursement request, would pegvaliase be accessed when patients have baseline blood Phe levels $600 \mu\text{mol/L}$ or higher for at least 6 months, despite adherence with treatment of sapropterin + Phe-restricted diet? What would be required as confirmation of Phe concentration $600 \mu\text{mol/L}$ or higher (e.g., one measurement in the last 30 days prior to treatment initiation)?</p>	<p>The clinical experts indicated that Canadian PKU treatment centres currently use the US guidelines (recommended Phe range for all ages 120 to $360 \mu\text{mol/L}$).</p>
<p>The ACMG guidelines state that the goal of treatment is to maintain Phe concentration in the range of 120 to $360 \mu\text{mol/L}$. European guidelines state that the primary goal of treatment is normal neurocognitive and psychosocial functioning through maintaining phenylalanine concentrations between 120 and $360 \mu\text{mol/L}$ up to the age of 12 years and up to $600 \mu\text{mol/L}$ thereafter. There are no Canadian guidelines; however, the Canadian management of PKU is generally more aligned with the ACMG treatment guidelines (sponsor's Clinical Summary).</p>	
<p>How would patients with blood Phe levels between 360 and $600 \mu\text{mol/L}$ be managed depending on the current Canadian standard of practice and the patient's clinical picture?</p>	
<p>The reimbursement request is for patients 16 years and older. What about those who are less than 16 years of age?</p>	<p>The Health Canada indication specifies that pegvaliase is only to be used in patients 16 years of age and older. The clinical experts were also not aware of robust studies of pegvaliase in patients younger than 16 years.</p>

Implementation Issues	Clinical Experts' Response
<p>Can the clinical experts provide some guidance into how pegvaliase will be managed during pregnancy (unplanned and planned)?</p>	<p>The product monograph advises against use of pegvaliase in pregnant women. The clinical experts consulted by CADTH pointed to a published anecdotal report that suggests that use of pegvaliase during pregnancy is potentially dangerous due to low Phe levels which have the potential to compromise fetal growth. The clinical experts believed that, in general, Phe control in women with PKU during pregnancy must be liberalized to prevent periods of very low Phe levels. CDEC agreed that pegvaliase should be administered to patients with PKU in accordance with the contraindications and precautions that outlined in the Product Monograph.</p>
<p>Would it be possible to clarify “existing management” prior to accessing pegvaliase? e.g., sapropterin + restricted diet vs. restricted diet. With the reimbursement request, it looks like pegvaliase is second line (first line perhaps being sapropterin). What is the place in therapy for pegvaliase (medication naïve versus medication experienced)?</p>	<p>Clinical experts indicated that sapropterin has an entirely different mechanism of action that is dependent upon PAH genotype. Pegvaliase works regardless of PAH genotype, while responsiveness to sapropterin is genotype-dependent based on residual enzyme activity and responsive to biopterin.</p> <p>CDEC acknowledged that sapropterin use prior to treatment with pegvaliase in sapropterin-responsive patients (based on PAH genotype) may be appropriate.</p>
<p>Discontinuation of pegvaliase decreased after the first 6 months of treatment (50 participants discontinued in the first 6 months and an additional 50 participants discontinued for the duration of the study). Forty patients (15.3%) discontinued due to adverse events – the most common adverse events leading to discontinuation were anaphylaxis, arthralgia, injection site reactions, and generalized rash.</p> <p>For patients who have experienced anaphylaxis while on treatment with pegvaliase, can re-treatment be considered?</p> <p>Would patients who experienced other adverse events that led to discontinuation be eligible for re-treatment? If so, is there a time frame by which this request should be made?</p> <p>For patients who are planning for pregnancy, at what point would they be eligible for retreatment?</p>	<p>Clinical experts noted that pegvaliase desensitization has been described anecdotally in published studies, but that retreatment would probably be contraindicated for patients who experience anaphylaxis. Patients who experience other (non-anaphylaxis) adverse events might be retreated but retreatment and its timeframe would depend on the nature and severity of the reaction.</p> <p>Clinical experts noted that pregnant women should be able to restart pegvaliase immediately after giving birth as they believed the risk for lactating mothers appeared to be very low.</p>
<p>Currently, sapropterin is the only medication available for the treatment of PKU. Though the inclusion criteria in the trials for sapropterin and pegvaliase may not be similar, should we consider alignment with the elements of the reimbursement criteria for sapropterin? e.g., requirement of blood Phe levels, requirement for Phe-restricted diet, managed by a specialist in metabolic/biochemical diseases.</p>	<p>CDEC noted that funding decisions for pegvaliase should be made based on the criteria listed in Table 1 (Reimbursement Conditions and Reasons) which are aligned with the evidence reviewed for pegvaliase.</p>
<p>Considerations for continuation or renewal of therapy</p> <p>There is a need for regular monitoring of Phe levels (once a month – is there a fasting and postprandial requirement?) until maintenance dose is established. Once the maintenance dose is established, periodic blood Phe</p>	<p>Clinical experts noted that clinicians do not generally insist on timing of Phe levels to meals because the diurnal fluctuation of Phe is unpredictable.</p>

Implementation Issues	Clinical Experts' Response
<p>monitoring is recommended to assess control in blood Phe levels. Are blood Phe levels easily accessible within the jurisdictions (e.g., Life Labs, etc.)?</p>	<p>According to the clinical experts, blood Phe levels are easily monitored using home dried blood spot, which is provided by the clinic and covered by plans.</p>
<p>Currently, sapropterin is the only medication available for the treatment of PKU. Would we consider alignment with the elements of the reimbursement criteria for renewal for sapropterin? e.g., what % decrease in blood Phe levels given the patient's pre-treatment level on existing therapy given a dose and treatment duration.</p> <p>How would a therapeutic response be defined in the context of pegvaliase?</p>	<p>Clinical experts believed that response to treatment, as assessed by serum phenylalanine levels, would likely be a poor criterion to consider. The Phe levels may be highly variable and can only be interpreted in conjunction with an assessment of the patient's existing diet and adherence to treatment. Clinical experts also noted that a therapeutic response should be defined by increased natural protein tolerance.</p> <p>CDEC noted that funding decisions for pegvaliase should be made based on the criteria listed in Table 1 (Reimbursement Conditions and Reasons) which are aligned with the evidence reviewed for pegvaliase.</p>
Considerations for discontinuation of therapy	
<p>What are the parameters that would be considered when describing loss of response, or absence of clinical benefit with pegvaliase in this population? For example, parameters such as blood Phe concentration (which appears to be related to dose, treatment duration and individual immune response), lack of normalization of diet, patient's HRQoL, patient's cognitive function, tolerability, etc.</p> <p>As per the draft product monograph, time to response which is achieving blood Phe levels $\leq 600 \mu\text{mol/L}$ varies among patients. The draft product monograph states to discontinue pegvaliase in patients who have not achieved an adequate response (how is an inadequate response defined?) after 48 weeks of continuous treatment with the maximum dosage of 60 mg once per day. The physician may decide, with the patient, to continue pegvaliase treatment in those patients who show other beneficial effects (e.g., ability to increase protein intake from intact food or improvement of neurocognitive symptoms).</p>	<p>According to the clinical experts consulted by CADTH, high Phe levels or significant adverse reactions are indicators of loss of response to or absence of clinical benefit from pegvaliase, most commonly due to poor compliance with administration of the medication. Clinical experts also indicated that the ability to increase protein intake should be a criterion for defining therapeutic response. CDEC acknowledged that blood Phe levels should be interpreted in conjunction with assessment of dietary adherence.</p> <p>The clinical experts felt that a period of 48 weeks is far too long to continue the medication with no evidence of benefit. Most often a 16-week period (induction/titration/part of maintenance) would be sufficient to establish suitability of treatment.</p>
<p>Is there any guidance on treatment interruptions with regards to dose recommendations based on the when the last dose of pegvaliase was administered? e.g., restart previous dose, restart with induction and titration schedule?</p>	<p>Clinical experts believed that, in most cases, restarting the previous dose would be acceptable.</p> <p>CDEC noted that the dose administration of pegvaliase should be in accordance with precautions outlined in the Product Monograph.</p>
Considerations for prescribing of therapy	
<p>See draft product monograph for recommended induction, titration and maintenance dosing.</p> <p>For patients who do not have a trained observer to accompany them for at least 1 hour following each injection during induction and titration, would they continue receiving injections at the clinic? Clinic visits may incur travel expense (induction – fixed dose; titration - uncertain duration dependent on patient's tolerability).</p>	<p>Clinical experts noted that, although in-clinic observation can be associated with additional expenses, there must be a trained observer present. The PRISM trials (including PRISM-2 RDT) required a competent observer to be present for all injections.</p> <p>The Health Canada Product Monograph for pegvaliase requires that initial administration(s) of pegvaliase "be performed under supervision of a health professional and patients should be</p>

Implementation Issues	Clinical Experts' Response
<p>Depending on the blood Phe levels achieved, is there a possibility for the patient to administer pegvaliase less than once daily during maintenance (e.g., twice weekly, four times weekly)?</p>	<p>closely observed for at least 1 hour following each of these initial injection(s)". The Product Monograph also requires a trained observer to be present for each pegvaliase administration for at least the first 6 months of treatment when the patient is self-injecting.</p> <p>The clinical experts agreed that in practice the drug could be titrated to the desired effect. Low Phe values are not safe for patients adherent to a rigorous diet); therefore, reducing the schedule for patients with low values is appropriate.</p>
<p>Would patients be able to easily access specialists who manage patients with PKU such as physicians and dietitians with expertise in metabolic disorders?</p>	<p>Clinical experts indicated that access to physicians might be challenging for patients who do not live in metropolitan centers. However, increasingly more clinics are organized in virtual format, because of the COVID-19 pandemic, that offer telehealth clinic visits. CDEC agreed that telehealth clinic visits would facilitate access to specialists and dietitians for PKU patients who undergo treatment with pegvaliase.</p>
<p>Are there any clinical situations in which the combination treatment of sapropterin and pegvaliase would be appropriate?</p> <p>Also, the product monograph states that two patients receiving concomitant injections of medroxyprogesterone acetate suspension containing PEG experienced hypersensitivity reactions. Are there implementation considerations regarding possible recommendations for this population?</p>	<p>CDEC noted that it did not review any evidence to show efficacy and safety of concomitant use of pegvaliase with sapropterin.</p> <p>CDEC acknowledged the statement included in the Product Monograph about a potential for anti-PEG antibody binding and increased risk of hypersensitivity to other PEGylated/PEG-containing therapeutics and noted that the management of severe adverse events should be in accordance with precautions outlined in the Product Monograph, and at the discretion of treating physician.</p>
Generalizability	
<p>As per the sponsor's estimation, █ patients with PKU out of an estimated █ patients nationally are 16 years and older with PKU being managed. What proportion of these patients are currently being treated with sapropterin? What number of patients are not controlled on sapropterin + diet? This would inform number of patients that may switch to pegvaliase.</p>	<p>Clinical experts estimated that <10% of adult patients with PKU would be on sapropterin (and dietary restriction) because no more than 25% of the PKU population have a genotype that causes sapropterin- sensitive disease. For the small proportion where sapropterin may have benefit there is limited availability. The clinical experts noted that compassionate access is being slowly discontinued. Among patients 16 years of age or older, approximately 90% of those on sapropterin and diet may not have controlled Phe (generally defined as 120 to 360 µmol/L).</p>
Care provision issues	
<p>The medication may be started in a hospital setting, while maintenance therapy could be provided in the community setting. Considerations may include that the patient is able to communicate issues associated with adverse events, is able to self-inject, has a trained observer to accompany them for at least 1 hour after each administration for at least the first 6 months of treatment, and have access to emergency services.</p>	<p>CDEC acknowledged the drug plans' input.</p>

Implementation Issues	Clinical Experts' Response
<p>Pegvaliase is stored refrigerated (2 to 8 degrees Celsius) but may be stored in its sealed tray at room temperature (20 to 25 degrees Celsius) for up to 30 days with protection from sources of heat. After removal from refrigeration, the product must not be returned to the refrigerator. How will it be dispensed re: cooling storage container?</p>	<p>CDEC noted that the storage and handling of pegvaliase should be in accordance with the manufacturer's specifications.</p>
<p>Premedication is recommended prior to each dose administered during induction and titration. Due to the potential for an acute systemic hypersensitivity reaction, monitoring and managing may be needed in the hospital setting.</p>	<p>CDEC noted that pre-treatment requirements, dose administration, and managing adverse events of pegvaliase should be in accordance with precautions outlined in the Product Monograph.</p>
System and economic issues	
<p>Existing patients may be switched to pegvaliase as per the reimbursement request; however, what about new patients who are not currently managed with sapropterin + diet? Does the anticipated budget impact only take into consideration the shift from sapropterin + diet?</p>	<p>CDEC recommends that pegvaliase be reimbursed for the treatment of patients PKU aged 16 years and older who have inadequate blood Phe levels greater than 600 µmol/L despite dietary management (aligned with Health Canada indication). The recommendation is not restricted to patients who have received or being treated with sapropterin.</p> <p>Clinical experts noted that all patients with PKU are prescribed dietary restriction.</p>
<p>Costs include drug acquisition and administration costs, Phe-restricted diet and formula costs, test and medical visit costs, premedication costs, and adverse event costs. What about loss of productivity costs dependent on patient's health state and costs related to patient's comorbidities?</p>	<p>Clinical experts believed that these could be considered as benefits rather than costs if treatment leads to improved health state. Loss of productivity related to adverse reactions to pegvaliase would, in most cases, be a minor consideration.</p>
<p>Sapropterin has successfully gone through price negotiations (concluded with an LOI Feb 13, 2020: https://www.pcpacanada.ca/negotiation/20957).</p>	<p>CDEC acknowledged the drug plans' input.</p>

ACMG = American College of Medical Genetics and Genomics; BH₄ = tetrahydrobiopterin; CDEC = Canadian Drug Expert Committee; EU = European Union; HRQoL = health-related quality of life; LOI = letter of intent; NB = New Brunswick; NIHB = non-insured health benefit; ON = Ontario; PAH = phenylalanine hydroxylase; PEG = polyethylene glycol; Phe = phenylalanine; PKU = phenylketonuria; SK = Saskatchewan; US = United States.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

PRISM-2 was a phase III, four-part, four-arm, double blind, placebo-controlled RDT with an extension period of open label (OL) treatment. The major feeder study for PRISM-2 was PRISM-1, a phase III, OL study to assess the safety and tolerability of two pegvaliase dose regimens (20 mg or 40 mg once daily; see Other Relevant Evidence); the main eligibility criteria for feeder studies were patients with PKU aged ≥16 years with blood Phe levels ≥600 µmol/L who were able to maintain a consistent diet. Dietary Phe control and adherence to MNT was not a requirement for participation in feeder studies or PRISM-2. Following enrolment and screening at 29 centers in the US, patients either entered Part 1 (OL Phe assessment) or directly into Part 4 (OL extension). In Part 1 (N=164), patients were randomized in a 1:1 ratio to receive OL pegvaliase (20 mg or 40 mg once daily, vial and syringe) for up to 13 weeks; blood Phe levels were measured every 2 weeks. Patients who achieved a mean blood Phe reduction of ≥ 20% from treatment-naïve baseline and were able to maintain their randomized pegvaliase dose were eligible for inclusion in the Part 2 (i.e., RDT) modified intention to treat (mITT) set, while those who did not achieve this degree of Phe reduction or were unable to maintain their randomized pegvaliase dose due to AEs transitioned directly to Part 4 (OL extension). In Part 2 (RDT; N=95), patients in each dose group (20 mg or 40 mg once daily, vial and syringe) were randomized 2:1 to either continue receiving their assigned dose of

pegvaliase or to receive a matching-administration placebo over 8 weeks of double blind treatment. In Part 3 (N=89), patients who completed Part 2 received OL pegvaliase (dose as assigned in Part 1) in two formats (vial and syringe or prefilled syringe) for 6 weeks and pharmacokinetics and pharmacodynamics (PK/PD) were compared. Part 4 (N=202) was an OL extension in which patients received OL pegvaliase (up to 60 mg once daily, prefilled syringe) for up to 274 weeks. Only data for the Part 2 RDT of the PRISM-2 study are described in the Systematic Review section of this report.

The primary objective of the PRISM-2 study was to evaluate the efficacy of pegvaliase in decreasing blood Phe levels by observing changes from the RDT baseline to RDT Week 8 in patients previously exposed to pegvaliase who were administered either pegvaliase (20 or 40 mg/day) or a matching-administration placebo in the RDT. Secondary objectives (all hierarchically tested) included comparing changes in Attention Deficit Hyperactivity Disorder Response Scale (Investigator-Rated) (ADHD RS-IV) Inattention subscale scores (among participants with drug-naïve baseline scores >9 as well as all participants), PKU-Specific Profile of Mood States (PKU POMS) (Self-Rated) Confusion subscale scores, PKU POMS (Self-Rated) total mood dysfunction (TMD) scores, and Profile of Mood States (POMS) (Self-Rated) TMD scores from Part 2 baseline to Part 2 Week 8 among patients previously exposed to pegvaliase who were randomized to receive either pegvaliase (20 or 40 mg/day) or a matching placebo in the RDT.

Almost all patients in PRISM-2 were White adults aged ≥18 years; the average age was approximately 30 years. According to the clinical experts consulted by CADTH for this review, baseline blood Phe, mood and inattention symptoms, and protein intake in the PRISM-2 study population were as expected for adult PKU patients with poor or no Phe control and limited adherence to MNT.

Efficacy Results

A poolability assessment of the two placebo groups (20 mg/day and 40 mg/day) indicated that the magnitude of blood Phe increase from Part 2 baseline to Part 2 Week 8 differed between the two placebo groups; therefore, the primary and secondary efficacy analyses were conducted by comparing the pooled active group (patients who continued on their assigned dose of pegvaliase from Part 1 in the Part 2 RDT) versus the 20 mg/day placebo group and the 40 mg/day placebo group separately. At Part 2 Week 8 and in the mITT set, the least squares mean (LSM) change in blood Phe level from Part 2 baseline was 26.50 µmol/L (95% confidence interval [CI], -68.26 to 121.26 µmol/L) in the pooled active group, 949.75 µmol/L (95% CI, 760.38 to 1139.11 µmol/L) in the 20 mg/day placebo group, and 664.77 µmol/L (95% CI, 465.45 to 864.10 µmol/L) in the 40 mg/day placebo group. The difference in LSM change from baseline comparing the pooled active group to the 20 mg/day placebo group was -923.25 µmol/L (95% CI, -1135.04 to -711.46 µmol/L) ($P<0.0001$). The difference in LSM change from baseline comparing the pooled active group to the 40 mg/day placebo group was -638.27 µmol/L (95% CI, -858.97 to -417.57 µmol/L) ($P<0.0001$). A cumulative distribution function analysis showed that at Part 2 Week 8 in the pooled active group, █ of patients had blood Phe ≤120 µmol/L while approximately █ had blood Phe between 600 µmol/L and 1200 µmol/L and approximately █ had blood Phe ≥1200 µmol/L. By contrast, in the placebo groups, no patients had blood Phe ≤120 µmol/L, while approximately █ had blood Phe between 600 µmol/L and 1200 µmol/L and approximately █ had blood Phe ≥1200 µmol/L.

No statistically significant differences were observed between treatment groups in ADHD RS-IV Inattention subscale scores among participants with drug-naïve baseline scores >9 and further statistical testing for other neurocognitive or neuropsychiatric symptoms (ADHD RS-IV Inattention subscale scores among all participants, PKU POMS [Self-Rated] Confusion subscale scores, PKU POMS [Self-Rated] TMD scores, and POMS [Self-Rated] TMD scores) was halted due to the hierarchical testing procedure. Changes in protein intake and HRQoL were not evaluated in PRISM-2 RDT.

Harms Results

Adverse events (AEs) were reported for the pooled active group (patients who continued to receive either 20 mg/day or 40 mg/day pegvaliase during the RDT) and the pooled placebo group (patients who receive either 20 mg/day or 40 mg/day pegvaliase in Part 1 and then switched to placebo during the RDT), as well as in some cases for individual dose groups. In PRISM-2 RDT, 83.3% of patients receiving active pegvaliase and 93.1% of patients receiving placebo experienced adverse events (AEs). Common AEs in both the pooled active and pooled placebo arms were arthralgia (pooled active 13.6% and pooled placebo 10.3%), headache (pooled active 12.1% and pooled placebo 24.1%), fatigue (pooled active 10.6% and pooled placebo 10.3%), anxiety (pooled active 10.6% and pooled placebo 6.9%), and injection site bruising (pooled active 4.5% and pooled placebo 10.3%). Serious AEs (SAEs) occurred in 2 patients (3.0%) receiving active pegvaliase and one patient (3.4%) receiving placebo. AEs leading to dose reduction or

interruption occurred in one patient (1.5%) receiving pegvaliase and one patient (3.4%) receiving placebo. No patients in PRISM-2 RDT had AEs leading to discontinuation of study drug. No deaths occurred during PRISM-2 RDT.

Several study protocol-defined adverse events of special interest (AESIs) occurred more frequently in patients receiving active pegvaliase than in those receiving placebo. These included hypersensitivity AEs (HAEs) (pooled active 39.4% and pooled placebo 13.8%), generalized skin reaction ≥ 14 days in duration (pooled active 10.6% and pooled placebo 0%), and injection site skin reaction ≥ 14 days in duration (pooled active 7.6% and pooled placebo 3.4%). Arthralgia and injection site reactions occurred at similar frequencies in patients receiving active pegvaliase (arthralgia: 13.6%; injection site reaction: 24.2%) and in those receiving placebo (arthralgia: 10.3%; injection site reaction: 24.1%). Among notable harms identified for this review, those occurring more frequently in patients receiving active pegvaliase than in those receiving placebo were rash (pooled active 7.6% and pooled placebo 3.4%), urticaria (pooled active [REDACTED] and pooled placebo [REDACTED]), pruritis (pooled active 7.6% and pooled placebo 3.4%), injection site pruritis (pooled active [REDACTED] and pooled placebo [REDACTED]), diarrhea (pooled active [REDACTED] and pooled placebo [REDACTED]), injection site erythema (pooled active [REDACTED] and pooled placebo [REDACTED]), and erythema (pooled active [REDACTED] and pooled placebo [REDACTED]). No anaphylaxis events or systemic hypersensitivity reactions occurred during PRISM-2 RDT.

Critical Appraisal

A major limitation of PRISM-2 RDT was the small size of the study and associated uncertainty. In addition, internal validity concerns included bias inherent to the RDT design (recruitment of a population of patients who did not discontinue treatment in feeder studies or PRISM-2 Part 1 due to AEs or patient preference, who were able to achieve target dose in feeder studies, and who achieved a $\geq 20\%$ decrease in blood Phe during PRISM-2 Part 1), baseline imbalances between treatment groups in gender, BMI, mean blood Phe level, protein intake, and inattention and mood symptoms, uncertainty regarding the measurement properties or minimal important differences (MIDs) of any of the efficacy outcomes used in the study (and associated uncertainty regarding the connection between changes in blood Phe at Part 2 Week 8 and other outcomes including inattention and mood symptoms, protein tolerance, diet liberalization, and HRQoL), and uncertainty in adherence to pegvaliase and consistency in dietary protein intake, both of which were self-reported.

There was some uncertainty in the target population of adult PKU patients most appropriate for pegvaliase and the degree of generalizability of the PRISM-2 RDT results to this population. The study recruited patients with uncontrolled Phe who were willing and able to self-administer pegvaliase. Changes in blood Phe observed in the study would not be generalizable to patients with good Phe control, although the clinical experts consulted by CADTH for this review felt that these patients would still be likely to benefit from treatment. The primary analysis of blood Phe may also not be generalizable to the general population of adult patients with PKU, which according to the clinical experts, includes many patients who will not comply with any therapy including pegvaliase. The specific relevance of pegvaliase-induced changes in blood Phe levels in the PRISM-2 RDT, measured at one or a few time points, to improvements in dietary protein tolerance, neurocognitive and neuropsychiatric symptoms, and HRQoL, was uncertain. According to the clinical experts consulted by CADTH for this review, blood Phe measurements are highly variable in PKU patients and the point estimate of Phe control associated with pegvaliase treatment at Part 2 Week 8 of PRISM-2 provided no randomized trial evidence on duration or consistency of Phe control in patients.

Indirect Comparisons

No indirect evidence was identified for this review.

Other Relevant Evidence

PRISM-1

PRISM-1 was a phase III, OL, randomized, multicenter study to assess the safety and tolerability of pegvaliase among drug-naïve PKU patients (N=261). PRISM-1 was the major feeder study for PRISM-2. The study is briefly summarized here to provide context for the patient population enrolled in PRISM-2, since 203/215 (94.4%) of patients participating in PRISM-2 entered from PRISM-1, as well as to contribute additional safety data. The primary objective of PRISM-1 was to characterize the safety and tolerability of induction, titration, and maintenance dosing in pegvaliase-naïve PKU patients who self-administered pegvaliase up to 20 mg/day or 40 mg/day. PKU patients aged 16 years or older were eligible to participate if they have blood Phe ≥ 600 $\mu\text{mol/L}$ and had not been

previously exposed to pegvaliase. Patients were randomized 1:1 to receive up to 20 mg/day or 40 mg/day pegvaliase for up to 36 weeks. Both randomized dose groups experienced reductions from baseline blood Phe levels. The mean (standard deviation [SD]) blood Phe concentration at baseline was 1232.7 (386.36) µmol/L in the ITT set and the mean (SD) reduction from baseline was █ µmol/L at Week 28 (n=133) and █ µmol/L at Week 36 (n=80). Almost all patients (99.6%) experienced AEs, most commonly arthralgia (65.1%), injection site reactions (56.7%), injection site erythema (45.2%), headache (31.4%), rash (25.7%), injection site pruritis (24.9%), and injection site pain (21.5%). SAEs occurred in 10.0% of patients; the most common SAE was anaphylaxis (3.1%). Anaphylaxis per the National Institute of Allergy and Infectious Diseases (NIAID)/Food Allergy and Anaphylaxis Network (FAAN) criteria occurred in 6.9% of patients and anaphylaxis per NIAID/FAAN criteria meeting Brown's severe criteria occurred in 1.5% of patients. Most patients (88.1%) experienced HAEs including arthralgia (65.1%), generalized skin reaction ≥14 days (22.6%), injection site reactions (86.2%), injection site skin reactions ≥14 days (26.4%), serum sickness (3.1%), and angioedema (35.6%).

PRISM-2

Evidence from the non-RDT portions of PRISM-2, including the Part 4 OL extension (N=215), is briefly summarized here to provide insight into the long-term safety of pegvaliase treatment (including doses up to 60 mg/day in the Part 4 OL extension). In PRISM-2, patients were treated with OL pegvaliase in Part 1 (20 mg/day or 40 mg/day, up to 13 weeks), Part 3 (20 mg/day or 40 mg/day, 6 weeks), and Part 4 (up to 60 mg/day, up to 274 weeks). In all parts of the study, self-reported adherence to pegvaliase was high with good exposure. In the overall PRISM-2 study, █ of patients receiving OL pegvaliase experienced AEs and █ of patients experienced SAEs, the majority of which occurred during the OL extension. No deaths occurred in the overall PRISM-2 study. Approximately █ of patients experienced AEs leading to pegvaliase dose reduction or interruption but only █ of patients experienced AEs leading to pegvaliase discontinuation. Most patients █ experienced HAEs. Approximately █ of patients █ experienced injection site reactions, approximately █ experience arthralgia, and nearly █ each) experienced generalized skin reactions ≥14 days in duration and injection site skin reactions ≥14 days in duration. Anaphylaxis reactions occurred in █ of patients, acute systemic hypersensitivity reactions occurred in █ of patients, and angioedema occurred in █ of patients.

PRISM-3

PRISM-3 was an exploratory phase III substudy to evaluate executive function in adults with PKU participating in PRISM-2 (N=9). Although the study addressed outcomes (executive function and self-perception) that were not evaluated in PRISM-2, interpretation was limited by small sample size.

Comparative Evidence with Sapropterin and MNT

Zori et al. conducted a retrospective observational cohort study of adolescent and adult PKU patients receiving pegvaliase with or without MNT, sapropterin plus MNT, or MNT alone. A cohort of patients who received pegvaliase plus MNT in the phase II 165-205 trial or phase III PRISM studies (PRISM-1 and PRISM-2) were compared using a propensity score matching (PSM) approach with a historical control of patients who received sapropterin plus MNT or MNT alone who participated in the PKU Demographics, Outcome, and Safety (PKUDOS) registry. The outcomes evaluated in the study included change in blood Phe and natural protein intake after 1 and 2 years of treatment. Greater decreases in blood Phe levels and increases in protein intake from natural food were observed for pegvaliase-treated patients compared with patients receiving sapropterin plus MNT or MNT alone. However, because of numerous limitations in study design involving comparison with a historic control cohort, potential bias due to the non-randomized study design and PSM approach, and statistical limitations (exploratory analysis only), no clear conclusions could be drawn concerning the comparative effectiveness of pegvaliase, sapropterin plus MNT, and MNT alone.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	PKU patients aged 16 years and older with uncontrolled blood phenylalanine levels on existing management.
Treatment	Pegvaliase, 5 mg to 60 mg daily plus MNT
Submitted price	Pegvaliase: 2.5 mg/0.5 mL prefilled syringe: \$405.00 10 mg/0.5 mL prefilled syringe: \$405.00 20 mg/0.5 mL prefilled syringe: \$405.00
Treatment cost	Titration year: \$130,205 to \$260,615 per patient per year Maintenance years: \$147,825 to \$443,475 per patient per year
Comparators	<ul style="list-style-type: none"> • MNT alone (Phe-restricted diet with or without medical food) • Sapropterin dihydrochloride, 1500 mg daily plus MNT
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (84 years)
Key data source	PRISM clinical trials, propensity score matching study
Key limitations	<ul style="list-style-type: none"> • Comparative clinical efficacy was highly uncertain and lacked face validity due to limitations with the propensity score matched study informing transition probabilities. • The model structure does not adequately capture the condition in that a single measure of blood Phe is not sufficiently predictive of overall quality of life, blood Phe control was not related to adherence to therapy in the model, and discontinuation was not considered, greatly inflating the costs of sapropterin and pegvaliase. • Health state utilities did not meet face validity, as clinical experts indicated the utility of uncontrolled PKU (blood Phe \geq1200 $\mu\text{mol/L}$) was far lower than what has been reported for conditions commonly perceived as more severe. • The reimbursement request is not clinically appropriate, given the likelihood of response to sapropterin can be predicted based on PAH mutation genotype in some patients, and the populations of patients who would benefit from pegvaliase is broader than that of sapropterin. • Other assumptions and limitations impacting the results were also noted: <ul style="list-style-type: none"> ◦ Pegvaliase maintenance dosing was likely underestimated. ◦ Adherence to MNT was overestimated for sapropterin and pegvaliase. ◦ Patient starting age was inappropriately modelled.
CADTH reanalysis results	<ul style="list-style-type: none"> • Due to the highly uncertain nature of the data derived from the sponsor's propensity score matched study and due to the inappropriateness of the model structure, CADTH was unable to derive a base case analysis. Instead, an exploratory reanalysis was conducted that utilized more appropriate assumptions, though CADTH notes the magnitude of clinical benefit estimated for pegvaliase in this reanalysis may still be overestimated. • In CADTH's exploratory reanalysis, the following revisions were made: altered the health state utilities to more plausible differences in HRQoL, increased the average daily syringe use of pegvaliase in maintenance years, decreased MNT usage in the sapropterin and pegvaliase groups, and increased patient starting age.

Component	Description
	<ul style="list-style-type: none"> CADTH's exploratory analyses estimated that the ICER associated with pegvaliase plus MNT was \$1,923,797 per QALY (\$7,665,703 incremental costs; 3.98 incremental QALYs) compared to MNT alone. CADTH was unable to address the lack of robust comparative clinical data, the flawed model structure, the absence of discontinuation, or the potential inappropriateness of the reimbursement request. Therefore, estimates of cost-effectiveness for pegvaliase relative to its comparators are highly uncertain.

ICER = incremental cost-effectiveness ratio; LYs= life years; MNT = medical nutritional therapy; PKU = phenylketonuria; QALY = quality adjusted life years; $\mu\text{mol/L}$ = micromoles per litre

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis:

- The population is uncertain and does not represent the Health Canada indication.
- Pegvaliase dosing was inappropriately modelled to only incorporate maintenance dosing and excluded adherence.
- Sapropterin dosing did not include adherence.
- The inclusion of MNT costs are likely not appropriate for a drug plan payer perspective.
- Market share uptake for pegvaliase is uncertain.

CADTH reanalysis included incorporating a titration year and adherence for pegvaliase patients, incorporating adherence for sapropterin patients, and removing the cost of MNT from the base case. In the CADTH reanalysis, for patients with PKU 16 years of age or older and who have blood Phe levels above 600 $\mu\text{mol/L}$ despite previous treatment with sapropterin, the estimated budget impact for pegvaliase was \$3,646,043 in Year 1, \$6,501,441 in Year 2, and \$8,587,322 in Year 3, for a three-year total incremental cost of \$18,734,806.

Canadian Drug Expert Committee (CDEC) Information**Members of the Committee:**

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Meeting Date: May 25, 2022

Regrets

None

Conflicts of Interest

None