

5.09 PEGVALIASE,

Solution for injection 2.5 mg in 0.5 mL,

Solution for injection 10 mg in 0.5 mL,

Solution for injection 20 mg in 1 mL,

Palynziq[®],

BioMarin Pharmaceutical Australia Pty Ltd.

1 Purpose of submission

- 1.1 The Category 1 submission requested a General Schedule Authority Required listing for the treatment of hyperphenylalaninemia (HPA) due to phenylketonuria (PKU) in patients aged 16 years and over who are not responsive to sapropterin.
- 1.2 The sponsor also requested an extension to the existing sapropterin listing to allow adults with HPA due to PKU to access sapropterin responsiveness testing and, for those patients who are sapropterin-responsive, to access continuing treatment. The sponsor presented the two requests in the same document, while the evaluation, ESC Advice and PBAC Public Summary Documents (PSD) for each of the drugs are presented as separate documents (also refer to Item 6.09, sapropterin).
- 1.3 Listing was requested on the basis of a cost-utility analysis versus a phenylalanine (Phe)-restricted diet alone.
- 1.4 Key components of the clinical issue addressed by the submission are presented in Table 1.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Patients with HPA due to PKU who are ≥16 years old, have blood Phe levels ≥ 600 µmol/L, and who are not responsive to sapropterin initial treatment (failed to achieve a ≥30% reduction in blood-Phe from baseline).
Intervention	Pegvaliase administered as a SC injection at a maintenance dose of 20-60 mg daily after induction and titration per the pegvaliase product information
Comparator	Phe-restricted diet alone
Outcomes	<ul style="list-style-type: none"> Reduction in blood Phe levels to < 360 µmol/L Reduction in ADHD-RS inattention subscale score of ≥5 from pegvaliase-naïve baseline A composite outcome of achieving at least one of the above two outcomes
Clinical claim	In ≥16-year-old patients with HPA due to PKU who are not responsive to sapropterin, pegvaliase is superior in terms of effectiveness than a Phe-diet alone in reducing blood Phe levels to <360 µmol/L (and in improving ADHD-RS inattention subscale scores from baseline by ≤5) and is inferior in terms of safety.

Source: Table 1.1-1 (p5) of the submission

ADHD-RS = attention-deficit hyperactivity disorder rating scale; HPA = hyperphenylalaninemia; Phe = phenylalanine; PKU = phenylketonuria; SC = subcutaneous

2 Background

Registration status

- 2.1 Pegvaliase was TGA registered on 6th July 2021 for the treatment of patients with PKU aged 16 years and older who have inadequate blood phenylalanine control despite prior management with available treatment options.
- 2.2 There was no explicit definition of the term ‘prior management with available treatment options’ in the indication. However, the Advisory Committee on Medicines (ACM) advised that pegvaliase should be a third line treatment for those who have failed standard treatment, including sapropterin, if relevant, but also advised that the indication should not be restricted to those adhering to nutritional advice or who are unresponsive to, or unable to tolerate, sapropterin (p32, AusPAR pegvaliase November 2021).

Previous PBAC consideration

- 2.3 This is the first submission for pegvaliase considered by the PBAC.
For more detail on PBAC’s view, see section 7 PBAC outcome.

3 Requested listing

- 3.1 Secretariat suggested additions are in italics and deletions are in strikethrough.

Public Summary Document – July 2022 PBAC Meeting

Name, Restriction, Manner of administration and form	Max. Qty (units)	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
PEGVALIASE 1 x 2.5 mg pre-filled, sc injection	6	0	\$497.05 published \$ effective	PALYNZIQ	BioMarin
PEGVALIASE 1 x 10 mg pre-filled, sc injection	14	0	\$497.05 published \$ effective	PALYNZIQ	BioMarin
PEGVALIASE 1 x 20 mg pre-filled, sc injection	90	5	\$497.05 published \$ effective	PALYNZIQ	BioMarin
PEGVALIASE 10 x 20 mg pre-filled, sc injection	90	5	\$4,501.220 published \$ effective	PALYNZIQ	BioMarin
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction Type – assessment time by Services Australia – Method of obtaining authority approval (if Authority Required) <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online application avenues)					
Condition: Hyperphenylalaninemia (HPA)					
Indication: Hyperphenylalaninemia (HPA) due to phenylketonuria (PKU)					
Treatment Phase: Initial treatment (induction, titration, and maintenance) <i>within first 24 months</i>					
Clinical criteria:					
Patient must not have previously received PBS-subsidised treatment with this drug for this condition					
AND					
Patient must have a baseline blood phenylalanine level above 600 micromole per L					
AND					
Patient must have failed to achieve an adequate response to a trial of 7 days with sapropterin at a dose of 20 mg/kg, defined as a reduction in blood phenylalanine of at least 30% in accordance with the PBS restriction for sapropterin ('Initial treatment - responsiveness testing' and 'First continuing treatment')					
AND					
Treatment must not be in combination with sapropterin					
Treatment criteria:					
Must be treated by a metabolic physician					
AND					
<i>Patient must be undergoing treatment with this drug within the first 24 months of treatment (i.e. the time from the date of the first authority application to the date of this authority application must not exceed 18 months)</i>					
Population criteria:					
Patient must be at least 16 years of age					
Prescribing Instructions:					
Dietary phenylalanine intake must be maintained at a constant level during the treatment period.					
Patient may qualify for PBS-subsidised treatment under this restriction once only Patient must not receive more than 24 months of treatment under this restriction.					
At the time of the authority application, medical practitioners should request the appropriate quantity of prefilled syringes or prefilled pens <i>and the appropriate number of repeats</i> , based on the dose required and in accordance with the recommended dosing described in the pegvaliase Product Information					
A response to initial treatment must be assessed following a minimum of 21 weeks and up to 24 months of treatment so there is adequate time for patients to titrate up to the maximum dosage of 60 mg per day or maximum tolerated dose.					
A response to treatment with this drug is defined as at least one of: blood phenylalanine level below 360 micromole per L / clinically meaningful reduction in the inattention subscale of the ADHD-RS score, defined as a 5-point reduction in the inattention subscale (Spencer et al., 2010)					
Administrative Advice: Special pricing arrangements apply.					

Public Summary Document – July 2022 PBAC Meeting

Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
Caution: Treatment with pegvaliase is associated with acute systemic hypersensitivity reactions. Patients should be instructed to recognise the signs and symptoms of acute systemic hypersensitivity reactions, in the proper emergency use of the adrenaline injection device, and the requirement to seek immediate medical care.
Treatment Phase: <i>Continuing treatment (maintenance)-Maintenance treatment</i>
Clinical criteria:
Patient must have previously received PBS-subsidised treatment <i>under the Initial treatment (induction, titration, and maintenance) restriction with this drug for this condition,</i>
AND
Patient must have demonstrated a response to initial treatment with this drug, <i>assessed at a minimum of a minimum of 21 weeks and up to 24 months from commencing treatment with this drug,</i> defined as at least one of either: blood phenylalanine level below 360 micromole per L or clinically meaningful reduction in the inattention subscale of the ADHD-RS score
AND
Treatment must not be in combination with sapropterin
AND
<i>Patient must be undergoing regular phenylalanine testing and assessment of adherence to dietary modifications</i>
Treatment criteria:
Must be treated by a metabolic physician; OR Must be treated by a nurse practitioner experienced in the treatment of phenylketonuria in consultation with a metabolic physician
Prescribing Instructions:
At the time of the authority application, medical practitioners <i>prescribers</i> should request the appropriate quantity of prefilled syringes or prefilled pens, required to provide 26 weeks <i>6 months</i> of treatment at a dose of 60 mg per day or the patient's maximum tolerated dose.
A response to initial treatment, assessed at a minimum of a minimum of 21 weeks and up to 24 months from commencing treatment with this drug, is defined as at least one of either: blood phenylalanine level below 360 micromole per L / clinically meaningful reduction in the inattention subscale of the ADHD-RS score, <i>defined as a 5-point reduction in the inattention subscale (Spencer et al., 2010)</i>
<i>Blood phenylalanine levels must be based on measurements taken during stable periods of the condition. Dietary phenylalanine intake must be maintained at a constant level.</i>
Administrative Advice:
Special pricing arrangements apply.
Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
<i>No increase in the maximum quantity or number of units may be authorised.</i>
Caution: Treatment with pegvaliase is associated with acute systemic hypersensitivity reactions. Patients should be instructed to recognise the signs and symptoms of acute systemic hypersensitivity reactions, in the proper emergency use of the adrenaline injection device, and the requirement to seek immediate medical care.
Note: <i>The ADHD-RS inattention subscale, with adult prompts, can be calculated here https://www.qandadhd.com/Content/pdf/ADHD-RS-IV_Tear-Pad-with-Adult-Prompts.pdf It comprises the following nine items: carelessness; difficulty sustaining attention in activities; listening; follow through; organisation; avoids/dislikes tasks requiring sustained mental effort; loses important items; easily distractable; and forgetful in daily activities. The severity of symptoms is rated on a four-point scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe.</i>

3.2 The submission proposed a special pricing arrangement with a proposed effective AEMP of \$| per syringe, regardless of the dosage.

Response assessment

- 3.3 Under the proposed restriction, patients must register a response to initiation treatment within 21 to 104 weeks (i.e., up to two years) of commencing pegvaliase to be eligible for continuing treatment. However, based on the recommended titration regimen, it would only take 37 to 49 weeks to reach the maximum maintenance dose of 60 mg/day. The product information (PI) states that pegvaliase treatment should be reconsidered if a patient “does not reach a clinically relevant blood phenylalanine reduction after 18 months of treatment” (Pegvaliase PI, p6). A patient who does not achieve a clinical response to pegvaliase may potentially receive two years of treatment which may not be consistent with quality use of medicines and comes with a significant cost (e.g., the cost of pegvaliase for a patient who uses a 60 mg/day maintenance dose over two years, would be \$). The ESC considered that two years was an inappropriately long period of time for patients to be on treatment without assessing whether the benefits were outweighing the risks. The ESC considered that a shorter period for assessing response would be more appropriate.
- 3.4 The proposed restriction defines a response to pegvaliase as either: (a) blood-Phe < 360 µmol/L; or (b) the achievement of a clinically meaningful reduction from pegvaliase-naïve baseline in the ADHD-RS.
- 3.5 The evaluation considered that the definition of response based on blood-Phe level < 360 µmol/L may be reasonable as there is a consensus in the international treatment guidelines for PKU that levels ≥ 360 µmol/L require treatment (however it is noted this treatment could be dietary or pharmacological).
- 3.6 The Attention Deficit Hyperactivity Disorder Rating Scale (ADHD-RS) inattention subscale score is one component of the ADHD-RS and is a 9-item investigator rated assessment focusing only on inattention symptoms, with a total possible score ranging from 0 to 27, with a higher score indicating the presence of inattention symptoms. The submission proposed a minimally clinically important difference (MCID) of ≥ 5 point decrease/improvement from baseline. The restriction allows patients who achieve a ≥ 5 point reduction from baseline in the ADHD-RS inattention subscale score to continue treatment. The evaluation and ESC considered this may be inappropriate as the ADHD-RS inattention subscale score and the nominated MCID have not been validated for use in PKU patients, and the submission did not provide any comparative clinical data to support a claim of superiority in ADHD-RS inattention subscale score. Further, the ESC noted that the ADHD-RS inattention subscale is not referred to in many of the clinical guidance documents and prescribers may not be familiar with its use. Overall, the ESC considered that it would be inappropriate for the restriction to define response based on the ADHD-RS inattention subscale, independent of blood-Phe levels. The pre-PBAC response argued that the results from the PRISM trials showed that there was a temporal association between reductions in blood-Phe levels and reductions in the ADHD RS-IV IA subscale scores and therefore it is reasonable to use it as a measure of benefit in patients who have not yet achieved a blood-Phe ≤ 360 µmol/L. The pre-PBAC response also noted that in the sponsor hearing the

clinician noted that the ADHD-RS IA subscale is routinely used to assess and monitor attention deficit in psychiatric patients in Australian clinical practice.

- 3.7 Additionally, the evaluation considered that it may not be appropriate to require patients to demonstrate blood-Phe $< 360 \mu\text{mol/L}$ or ≥ 5 reduction in ADHD-RS inattention subscale score only once to meet the definition of initial response as PKU patients often undergo fluctuations in dietary restrictions which may temporally impact these outcome measurements.
- 3.8 In its consideration of sapropterin at the same meeting, the PBAC noted that consumers and clinicians had outlined that factors other than Phe levels may also be important markers of a meaningful improvement for patients, such as protein tolerance/dietary Phe intake, quality of life and an assessment as to how well a patient is managing with their current regimen. The PBAC had considered that a change to the definition of response for the sapropterin restrictions may be appropriate and noted that expert clinical consultation would be required in order to determine the most appropriate (if any) change to the response criterion (paragraph 3.5, sapropterin PBAC PSD, July 2022).

Limiting use to sapropterin non-responders

- 3.9 The requested restriction requires that the patient must have “failed to achieve an adequate response to a trial of 7 days with sapropterin at a dose of 20 mg/kg, defined as a reduction in blood phenylalanine of at least 30%”, which limits use of pegvaliase to a third-line population i.e., the subgroup of patients who are sapropterin non-responders.
- 3.10 The evaluation and the ESC considered that the targeting of only sapropterin non-responders may be inequitable and was not adequately justified in the submission, as it was not aligned with the enrolment criteria of the pivotal PRISM trial. Further, exploratory subgroup analyses between patients who were ‘sapropterin responders’ and ‘sapropterin non-responders’ (based on investigator determination) in PRISM 1/ PRISM 2 appear to suggest that there was no difference in efficacy between the two subgroups. However, results from this subgroup analysis had applicability issues to the proposed population given differences in the definition of sapropterin response. The Pre-Sub Committee Response (PSCR) stated that the submission requested listing only in sapropterin non-responders as this group has the highest clinical need. Further, the pre-PBAC response stated that, compared with sapropterin, pegvaliase has a less convenient route of administration (daily subcutaneous injections while sapropterin is an oral treatment), a much longer time before efficacy is observed with a titration period of up to 24 months, and a less favourable safety profile including a risk of hypersensitivity reactions.
- 3.11 Further, the proposed restriction excludes patients who are currently receiving sapropterin but who are responding sub-optimally (e.g., a patient may have had a $\geq 30\%$ reduction in Phe levels early in treatment but may not currently have Phe levels within the target range, particularly those patients with high baseline Phe levels). The

evaluation and the ESC considered that it was unclear if this is clinically appropriate. Further, the ESC further considered this may be inequitable.

- 3.12 Sapropterin (including access to sapropterin responsiveness testing) is currently only PBS-listed for initiation in patients aged < 18 years, but patients can continue use in adulthood if they commenced prior to 18 years of age. As outlined in paragraph 1.1, the sponsor also requested an extension to the existing sapropterin listing to allow patients ≥ 18 years to access sapropterin. Without this corresponding extension to the sapropterin listing, the prevalent pool of adult patients (i.e., those patients who were aged ≥ 18 years when sapropterin was PBS-listed) would have to access sapropterin privately prior to being able to access pegvaliase (under the restriction proposed by the sponsor which would limit use to sapropterin non-responders), which the ESC considered would lead to equity issues.

Other

- 3.13 Under continuing treatment, only 20 mg syringes are available. As such, continuing patients who have a maintenance dose that is not exactly 20 mg/day, 40 mg/day or 60 mg/day would be required to utilise the relevant proportion of an extra 20 mg dose (e.g., a 30 mg/day patient would require 2 x 20 mg syringes per day, with 10 mg of the second syringe not being utilised). This was appropriately incorporated in the resource-use of the economic model.
- 3.14 The requested restriction was narrower than the TGA approved indication, which did not:
- define what treatment options must have been used previously (the requested restriction specifies patients must fail to achieve ≥ 30% reduction from baseline in blood-Phe with a seven-day trial of sapropterin);
 - specify that a blood-Phe minimum of 600 µmol/L is required for treatment, however this was aligned with the enrolment criteria for the pivotal PRISM 1/PRISM 2 trial; and
 - specify that pegvaliase cannot be used with sapropterin.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 PKU is a rare inborn disorder which leads to HPA whereby patients suffer from elevated levels of the essential amino acid Phe in the blood. In patients with PKU, the enzyme phenylalanine hydroxylase (PAH) does not effectively metabolise Phe into the essential amino acid tyrosine due to mutations in the PAH gene causing PAH deficiency.
- 4.2 In adults, untreated high Phe-blood levels can cause neuropsychiatric symptoms including inattention, hyperactivity, anxiety, depression, seizures and tremors. This

can impact executive function, which is a collection of cognitive skills that are required to self-regulate and organise mental efforts in order to achieve goals (Bilder et al., 2016). The ability to plan and organise are critical skills required in adulthood, and poor executive function as a result of elevated blood Phe can have negative impacts on a person's employment and relationships, as well as their ability to appropriately manage their PKU.

- 4.3 The PBAC has previously considered that the benefits of sapropterin therapy in terms of improved neurological function were likely to be greatest during the development period for children and adolescents as untreated elevated blood-Phe levels during developmental stages can lead to cognitive impairment, neurocognitive deficits, behavioural abnormalities, seizures and other serious neurological complications (paragraphs 4.2, 7.1 and 7.3, sapropterin PSD, March 2018 PBAC meeting). In its consideration of pegvaliase, the ACM advised that in the real-world setting, behavioural and psychological manifestations of PKU are substantially reversible in adulthood with improvements in serum Phe concentrations (p30, AusPAR pegvaliase November 2021).
- 4.4 Patients often maintain their Phe-levels via a Phe-controlled diet, consisting of low-protein foods combined with PBS-subsidised Phe-free supplements. PKU patients experience negative quality-of-life (QoL) impacts through neuropsychiatric symptoms and executive functioning impacts, but also through the negative impacts of a Phe-restrictive diet.
- 4.5 Pegvaliase is a pegylated recombinant phenylalanine ammonia lyase enzyme derived from *Anabaena variabilis* bacteria. Pegvaliase is administered daily via a subcutaneous injection, with an up-titration schedule culminating with maintenance doses of between 20 mg to 60 mg daily depending on tolerance and response. Pegvaliase substitutes for the deficient PAH enzyme and therefore can be effective across all phenotype severities, including severe patients with no residual PAH activity. Therefore, response to pegvaliase is dependent on a patient's ability to tolerate immune responses to pegvaliase. Comparatively, sapropterin is a cofactor for PAH and is dependent on residual PAH efficiency, and patients who are most likely to respond to sapropterin are those with lower baseline Phe levels and 'milder' disease. The PSCR stated that pegvaliase is effective irrespective of prior sapropterin response because it is an enzyme substitution therapy, which unlike sapropterin, is not reliant on the patient having any residual endogenous PAH activity.
- 4.6 Pegvaliase is intended to be used in conjunction with a Phe-restricted diet. In clinical practice, it is likely that at least some of the benefits of pegvaliase will be due to a relaxation of dietary Phe-restrictions. For example, the ESC noted that Longo et al stated "The goal of pegvaliase treatment, therefore, is to provide life-long maintenance of blood Phe concentration as low as possible (concentrations of 31–120 µmol/L should not be regarded as too low) while normalizing diet (defined as not

requiring PKU medical food and containing at least the Dietary Reference Intake [DRI] for protein [0.8 g/kg/day]¹.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The submission appropriately nominated a Phe-restricted diet alone as the main comparator, consisting of a Phe-restricted dietary intake and PBS-listed Phe-free amino acid supplements. The main argument provided in support of this nomination was that the target population are sapropterin non-responders and there are no other pharmacological treatments for PKU.
- 5.2 Phe-restricted diet was also the nominated comparator in the most recent November 2020 resubmission for sapropterin in patients aged ≥ 18 years with maternal PKU and was considered by the PBAC as appropriate and consistent with previous submissions for PKU (paragraph 5.1, sapropterin PSD, November 2020 PBAC meeting).
- 5.3 The submission noted that, for consistency with previous PBAC submissions for sapropterin for the treatment of PKU, a Phe-restricted diet comprises the following:
- Natural protein restriction according to individual Phe tolerance;
 - PBS-listed Phe-free amino acid supplements (with added vitamins and minerals) to meet protein and non-protein requirements; and
 - Low-protein food to meet energy requirements.
- 5.4 The submission considered that all patients should be on a Phe-restricted diet, and consequently pegvaliase would not be expected to replace a Phe-restricted diet but would instead be used in combination with it. However, the submission also considered that adherence to the Phe-restricted diet tended to be low, consequently it was unclear whether pegvaliase would in practice, serve as a replacement. DUSC has previously considered that sapropterin use may allow inappropriate relaxation of the Phe-restricted diet (paragraph 6.70, sapropterin PSD, March 2018 PBAC meeting).
- 5.5 As discussed in paragraph 3.10, the evaluation and the ESC considered that the restriction of pegvaliase to sapropterin non-responders was poorly justified and may not be clinically appropriate. In practice it may be difficult to distinguish two separate lines of therapy e.g., there may be use of pegvaliase in patients who perceive that there will be efficacy benefits with pegvaliase that would allow increases to dietary Phe consumption. Should the clinical use of pegvaliase be broader than requested by the sponsor, sapropterin would likely be a comparator to pegvaliase.

For more detail on PBAC's view, see section 7 PBAC outcome.

¹ Longo N, Dimmock D, Levy H, et al. Evidence- and consensus-based recommendations for the use of pegvaliase in adults with phenylketonuria. *Genet Med.* 2019; 21(8):1851-1867. doi:10.1038/s41436-018-0403-z

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The two clinicians described the real world, functional impact of high Phe levels on patients including high rates of depression, anxiety and panic attacks and also the impacts on cognitive function in terms of reduced working memory, attention and mood. The clinicians stated that even small reductions in Phe levels can improve these outcomes and consequently improve patients' ability to manage their diet, daily life, family and work. One clinician noted that these outcomes are clinically evident but are difficult to study and were not well-captured in the trials.
- 6.2 One of the clinicians outlined that the ADHD-RS tool is commonly used in clinical practice. The clinician considered that it was suitable for capturing patient-reported, real-life outcomes that are important for measuring functional impairment.
- 6.3 One clinician noted that for some patients a long dose titration is needed and there is variable time to achieve efficacy. The clinician noted that this was due to unpredictable variation in patients' immune responses to pegvaliase. While slow titration is needed to minimise hypersensitivity reactions, some patients require high doses in order to overcome the antibodies that neutralise the drug.

Consumer comments

- 6.4 Representatives of the PBAC met with patient and health professional representatives prior to the PBAC meeting. The following is a summary of the perspectives presented:
- Diet management alone is extremely difficult and has an enormous impact on patients. Many patients struggle to lower or maintain their Phe levels using diet alone.
 - Dopamine depletion results in reduced executive function and serotonin depletion results in anxiety and depression, though cognitive function and psychiatric well-being impacts are experienced at variable levels.
 - Reductions in Phe levels in adults can lead to significant and meaningful improvements, with depression and anxiety scores improved and working memory and cognitive function substantially improved or returned over the longer term². Clinicians also highlighted that there is evidence that patients

² Burgess NM, Kelso W, Malpas CB, Winton-Brown T, Fazio T, Panetta J, De Jong G, Neath J, Atherton S, Velakoulis D, Walterfang M. The effect of improved dietary control on cognitive and psychiatric functioning in adults with phenylketonuria: the ReDAPT study. *Orphanet J Rare Dis.* 2021 Jan 18;16(1):35. doi: 10.1186/s13023-020-01668-2. PMID: 33461585; PMCID: PMC7814424.

experience reversible changes in white matter indicative of neurodegenerative effects of raised blood Phe levels³.

- The sponsor's proposed management algorithm, which positioned pegvaliase as a second-line treatment for those patients who are not responsive to sapropterin, was not considered to be appropriate.
- Treatment with sapropterin has been life-changing for some patients, while others have only experienced a minimal response in terms of meaningful changes to diet or effects on cognitive function, so there is a high clinical need for alternative treatment options.
- Blood Phe levels should not be the single measure of assessment for determining response to treatment or optimal therapy for overall patient benefit. Meaningful improvement could also be defined in terms of protein tolerance/dietary Phe intake, QoL and how well a patient manages on their current regimen.

- 6.5 Health professionals outlined that access to pegvaliase may be constrained by the availability of metabolic clinics given the level of monitoring required during the initiation and titration phases due to the potential for life-threatening adverse events and noting that clinics are already at capacity or do not exist in some states and Territories.
- 6.6 The PBAC noted and welcomed the contributions from health professionals (5), individuals (145) and organisations (3).
- 6.7 The Metabolic Dietary Disorders Association and PKU Association of NSW (MDDA & PKUNSW) noted the importance of equitable access to treatments for all Australians with PKU. The MDDA & PKUNSW noted that sapropterin and pegvaliase work differently and have different advantages and disadvantages. Decisions about which treatment a patient uses should be made by a clinician in consultation with the individual considering clinical need and personal circumstances. MDDA & PKUNSW were not supportive of the submission's proposal to restrict pegvaliase to patients who do not respond to sapropterin and considered this was not justified based on clinical outcomes.
- 6.8 The MDDA & PKUNSW also described the burden of the restrictive diet and complexity of managing PKU, the limitations and unsustainability of dietary management and the impact of PKU on every aspect of life.
- 6.9 Rare Voices Australia (RVA) stated that it is aware of the advantages of pegvaliase including its impact on: reducing blood Phe concentration; increasing natural protein tolerance; improving health outcomes and decreasing co-morbidities; improving quality of life and, importantly, improving neurocognitive functioning and mental wellbeing. RVA were also not supportive of restricting pegvaliase to patients who do

³ Anderson PJ, Leuzzi V. White matter pathology in phenylketonuria. *Mol Genet Metab.* 2010;99 Suppl 1:S3-9. doi: 10.1016/j.ymgme.2009.10.005. PMID: 20123467.

not respond to sapropterin, noting that there is variability in treatment response and some patients may miss out on treatments that have a greater benefit for them.

- 6.10 All comments from health professionals, individuals with PKU and other interested individuals were supportive of PBS listing of pegvaliase. Many parents and individuals with PKU spoke of the inequity of restricting access to pegvaliase to those who do not respond to sapropterin. The desire for equality of access to pegvaliase regardless of age was also discussed by many contributors.
- 6.11 Individuals who would like access to pegvaliase to treat their PKU, and the carers and supporters of those with PKU, discussed the difficulties of maintaining low Phe levels with dietary management and/or sapropterin. Even when the diet is strictly adhered to, this may be insufficient to maintain an acceptable Phe level. Monitoring the levels and making the necessary dietary adjustments in a timely fashion was also an issue for many. The comments also described issues with accessing food supplements and low protein foods in terms of cost and unreliable supply chains.
- 6.12 Some individuals with PKU reported that compliance to protein-restricted diets becomes more difficult as patients enter adulthood once they take responsibility for their own diet, as adherence is made more difficult due to the challenges of PKU (fatigue, brain fog, mood disturbance).
- 6.13 Health professionals discussed the potential efficacy associated with pegvaliase in terms of reducing blood-Phe levels and alleviating the effects of PKU. Consumers expressed high expectations of the effectiveness of pegvaliase at maintaining low Phe levels, which they hoped would enable them to live fuller lives with fewer symptoms, better cognition, improved physical and psychological health, greater social and economic engagement and a significantly reduced treatment burden.
- 6.14 The potential quality of life benefits for pegvaliase were strongly reinforced by patients and also their families and carers. This included improvements in psychosocial and cognitive function, energy levels, and managing self-care and tasks on a daily basis. The comments outlined that increased protein tolerance was an important outcome, as it enabled patients to eat a broader range of foods, alleviating the burden of living with a severely low protein diet.
- 6.15 Health professionals outlined concerns about the possible adverse effects of pegvaliase for some patients, however the majority of contributors felt these safety issues could be mitigated or were outweighed by the potential advantages.

Clinical trials and studies

- 6.16 The submission was based on an unanchored matched-adjusted historical cohort analysis (Zori 2019) and a naïve-indirect comparison using:
 - pegvaliase patient data from (a) one randomised trial which included an 8-week component that compared pegvaliase to placebo (PRISM 2) and (b) one

Public Summary Document – July 2022 PBAC Meeting

randomised trial that compared pegvaliase 20 mg/day to pegvaliase 40 mg/day (PRISM 1); and

- Data from the Phenylketonuria (PKU) Demographics, Outcomes and Safety (PKUDOS) study to inform the Phe-restricted diet alone arm.

6.17 The submission also presented a review of translational studies discussing the relationship between blood-Phe and improvements in neuropsychiatric symptoms; and Phe tolerance (increase in dietary Phe intake) with quality of life in adult PKU patients.

6.18 Details of the trials and studies presented in the submission are provided in Table 2.

Public Summary Document – July 2022 PBAC Meeting

Table 2: Trials, studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
PRISM 1	A Phase 3, open-label, randomized, multi-center study to assess the safety and tolerability of an induction, titration, and maintenance dose regimen of BMN 165 self-administered by adults with phenylketonuria not previously treated with BMN 165	March 2018
	A Phase 3, open-label, randomized, multi-center study to assess the safety and tolerability of an induction, titration, and maintenance dose regimen of BMN 165 self administered by adults with phenylketonuria not previously treated with BMN 165	August 2014
	Thomas et al, J. Pegvaliase for the treatment of phenylketonuria: Results of a long-term phase 3 clinical trial program (PRISM).	Mol Gen Metab, 2018; 124: 27-38
	Gupta, S. Association of immune response with efficacy and safety outcomes in adults with phenylketonuria administered pegvaliase in phase 3 clinical trials	EBioMedicine 2018; 37: 366-373
	Bilder, D. Improved attention linked to sustained phenylalanine reduction in adults with early-treated phenylketonuria	Am J Med Genet 2021; 1–11
	Aryal et al. M. Achieving efficacy in subjects with sustained pegvaliase-neutralizing antibody responses.	Mol Gen Metab 2021: 235-242
PRISM 2	A four-part, Phase 3, randomized, double-blind, placebo-controlled, four-arm, discontinuation study to evaluate the efficacy and safety of subcutaneous injections of BMN 165 self-administered by adults with phenylketonuria	October 2019
	A four-part, Phase 3, randomized, double-blind, placebo-controlled, four-arm, discontinuation study to evaluate the efficacy and safety of subcutaneous injections of BMN 165 self-administered by adults with phenylketonuria	March 2017
	Harding et al. C. Pegvaliase for the treatment of phenylketonuria: A pivotal, double-blind randomized discontinuation Phase 3 clinical trial.	Mol Gen Metab; 124: 20-26
	Thomas et al, J. Pegvaliase for the treatment of phenylketonuria: Results of a long-term phase 3 clinical trial program (PRISM).	Mol Gen Metab, 2018; 124: 27-38
	Gupta, S. Association of immune response with efficacy and safety outcomes in adults with phenylketonuria administered pegvaliase in phase 3 clinical trials	EBioMedicine 2018; 37: 366-373
	Bilder, D. Improved attention linked to sustained phenylalanine reduction in adults with early-treated phenylketonuria	Am J Med Genet 2021; 1–11
	Aryal et al. M. Achieving efficacy in subjects with sustained pegvaliase-neutralizing antibody responses.	Mol Gen Metab 2021: 235-242
Additional studies		
PKUDOS Registry	Longo, N. et al. Long-term safety and efficacy of sapropterin: The PKUDOS registry experience.	Mol Gen Metab, 2015; 114: 557-563
	Lilienstein, J. et al. Interim analysis of the Phenylketonuria (PKU) patients enrolled in the PKUDOS registry.	National PKU Alliance Conference: July 5-8, 2018, Atlanta, Georgia
Matched-adjusted comparison	Zori, R. et al. Long-term comparative effectiveness of pegvaliase versus standard of care comparators in adults with phenylketonuria	Mol Gen Metab 2019; 128: 92-101

Source: Table 2.2-1, pp53-4 of the submission & Table 2.8-10, pp175-6 of the submission

6.19 The key features of the included evidence are presented below.

Public Summary Document – July 2022 PBAC Meeting

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Pegvaliase 20 mg/day vs Pegvaliase 40 mg/day						
PRISM 1	261	R, OL, MC 26-35 weeks	High	PKU, Phe >600µmol/L, ≥18 years-old Patients who completed PRISM 2 Part 2	Blood-Phe; Dietary Phe intake; Psychiatric assessment; Safety As above; Pharmacodynamics	Yes (blood-Phe; response rate; safety)
PRISM 2 Part 1	164	R, OL, MC 13 weeks	High			
PRISM 2 Part 3	89	R, OL, MC 6 weeks	High			
Pegvaliase vs placebo						
PRISM 2 Part 2	95	R, DB, MC 8 weeks	High ^	PRISM 2 Part 1 patients who achieved ≥20% reduction in blood- Phe from pegvaliase-naïve baseline	As in PRISM 1	Yes (blood-Phe; response rate; safety)
Pegvaliase single-arm extension study						
PRISM 2 Part 4	202	MC, OL 274 weeks	High	PRISM 1, PRISM 2 Parts 1-3 patients	As in PRISM 1	Yes (blood-Phe; response rate; safety)
Phe-diet registry						
PKUDOS	715	MC, Registry	NA	PKU; previously received, receiving or intend to receive sapropterin	Blood-Phe; Dietary Phe intake; Psychiatric assessment; Safety	Yes (blood-Phe)
Pegvaliase vs Phe-restricted diet						
Zori 2019	250	Matched cohort analysis	High #	PRISM patients; PKUDOS patients who discontinued sapropterin; baseline blood-Phe ≥600 µmol/L; ≥18 years old	Blood-Phe; protein intake; Phe response rate; Safety	No
Indirect naïve comparison	311	Indirect naïve comparison	High *	PRISM patients; PKUDOS patients aged ≥18, previously treated with sapropterin, >600µmol/L	Blood-Phe; Phe response rate	Yes (blood-Phe)

Source: Section 2 of the submission

DB = double blind; MC = multi-centre; NA = not applicable; OL = open label; Phe = phenylalanine; R = randomised.

^ High risk of selection bias as only patients who achieved a ≥20% reduction in blood-Phe from pegvaliase-naïve baseline were included

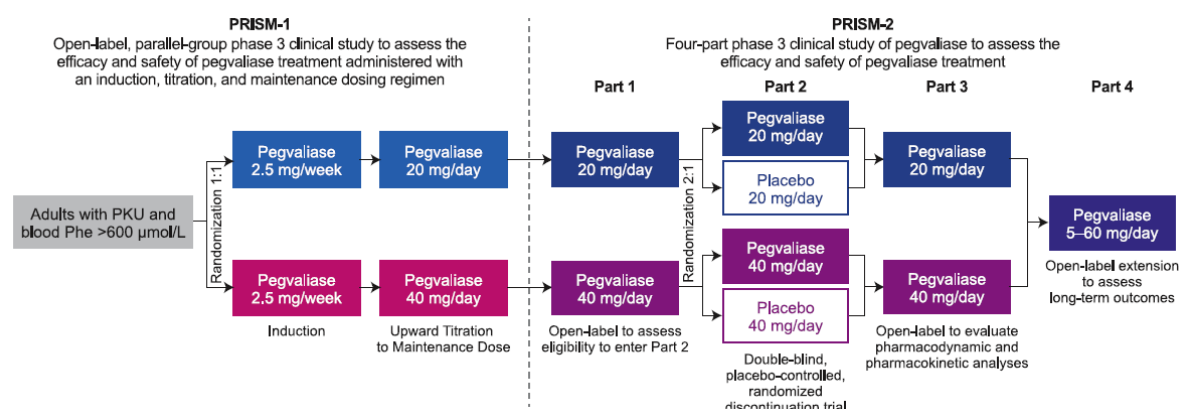
High risk of bias as lack of control in confounding from the open-label single arm design in the PRISM 1/PRISM 2 trials and the PKUDOS registry used to inform the comparison

* High risk of bias as no common comparator and lower ability to adequately assess and control for confounding variables.

6.20 PRISM 2 was a four-part clinical trial that varied in comparison groups and trial design, and enrolled patients from PRISM 1. The flow of patients through PRISM 1 and PRISM 2 is summarised in Figure 1. Other than PRISM 2 Part 2, all parts of the PRISM 1 and PRISM 2 trials were single arm, open-label studies and therefore associated with a high risk of bias. The evaluation and ESC considered that PRISM 2 Part 2 was

associated with a high risk of selection bias as only patients who achieved a $\geq 20\%$ reduction in blood-Phe from pegvaliase-naïve baseline were included, favouring pegvaliase. Further, the ESC noted that PRISM 2 Part 2 only included patients who had not discontinued pegvaliase in earlier studies (i.e., patients had already been taking pegvaliase for a considerable length of time) which was also likely to bias results in favour of pegvaliase.

Figure 1: PRISM 1 and PRISM 2 trial study designs



Note: Patients from the Phase 2 trials Study 165-205 and PAL-003 are able to enter PRISM 2 at Part 1 or at Part 4.

Source: Figure 2.3-1 (p56) of the submission

6.21 PKUDOS was a Phase 4 voluntary observational multi-centre registry study which included PKU patients who had previously received sapropterin therapy, were currently receiving sapropterin therapy or intended to receive sapropterin therapy. The submission relied on the subgroup of patients aged 18 years and above who had previously used but discontinued sapropterin, as a proxy for patients aged 18 and above who failed to respond to a seven-day trial of sapropterin and were treated with a Phe-restricted diet only. However, this included patients who had discontinued sapropterin for any reason and the reasons for discontinuation were not reported in the submission. It was unknown if these patients were sapropterin responders (as defined in the requested restriction), so the applicability of these data were unclear. Further, the ESC noted that the submission had not provided detailed information about the flow of patients through PKUDOS, but there appeared to be a high proportion of patients who were lost to follow-up over time.

6.22 Data from four separate PKUDOS data cuts were presented in the submission:

- Data cut-off of June 2013, which is reported in a journal article (Longo et al., 2015b). This had previously been considered by the PBAC;
- Data cut-off of May 2016 from a sponsor commissioned analysis of the subgroup of patients aged 18 years or older at first use of sapropterin who had a (pre-sapropterin) baseline Phe > 600 µmol/L. This had not been previously considered by the PBAC;
- Data cut-off of February 2017, which is reported as a conference poster (Lilienstein 2018). This had not been previously considered by the PBAC; and

- Data cut-off of February 2018, which was used in the matched-adjusted analysis reported in Zori 2019. This had not been previously considered by the PBAC.

6.23 The two comparisons presented in the submission (a naïve-indirect comparison; and an unanchored matched-adjusted analysis both) were based on data from the PRISM studies to inform the pegvaliase arm and the PKUDOS registry to inform the Phe-diet alone arm. The ESC considered that a key underlying issue with the comparisons was that neither included a common comparator arm.

Comparative effectiveness

6.24 The results for change in blood-Phe over time in PRISM 1 (Table 4) and PRISM 2 Part 2 (Table 5) are presented below.

Table 4: Results of change in blood-Phe over time in PRISM 1

	Pegvaliase 20 mg/day (N = 131)	Pegvaliase 40 mg/day (N = 130)	Pegvaliase 20 mg/day (N = 131)	Pegvaliase 40 mg/day (N = 130)
	Mean (SD), µmol/L	Mean (SD), µmol/L	Change from baseline*, mean (SD), µmol/L	Change from baseline*, mean (SD), µmol/L
Baseline	n = 131 1241.0 (389.7)	n = 130 1224.4 (384.3)	-	-
Week 12	n = 120 997.0 (513.84)	n = 120 859.1 (534.14)	n = 120 -264.2 (432.30)	n = 120 -359.9 (495.53)
Week 24	n = 76 929.2 (449.02)	n = 75 668.0 (547.94)	n = 76 -334.7 (438.30)	n = 75 -509.3 (619.20)
Week 36	n = 44 868.4 (501.78)	n = 36 624.4 (530.58)	n = 44 -356.4 (539.93)	n = 36 -524.6 (678.74)

Source: Table 2.5-1 (p98) of the submission

Phe = phenylalanine; SD = standard deviation

* Change from baseline was based on patients with available measurements at both time points.

Table 5: Results of change in blood-Phe over time in PRISM 2 Part 2

Outcome	Pooled pegvaliase N = 58	Placebo (20 mg/day pegvaliase previously in Part 1) [^] N = 14	Placebo (40 mg/day pegvaliase previously in Part 1) [^] N = 14
Mean (SD)			
Responder (blood-Phe ≤360µmol/L) #			
n/N (%)	25/49 (51)	0/13 (0)	0/10 (0)
Phe levels (µmol/L), Mean (SD)			
Baseline*	503.9 (520.28)	563.9 (504.62)	508.2 (363.68)
Week 8	559.2 (569.47)	1509.0 (372.64)	1164.4 (343.32)
Mean change from baseline	18.6 (279.43)	996.4 (555.0)	599.0 (507.40)
LS mean change from baseline (95% CI)	26.50 (-68.26, 121.26)	949.75 (760.38, 1139.11)	664.77 (465.45, 864.10)
Pooled pegvaliase vs placebo			
Difference in LS means (95% CI)	-	-923.25 (-1135.04, -711.46) p < 0.0001~	-638.27 (-858.97, -417.57) p < 0.0001~

Source: Table 2.5-5 (p108) of the submission, table 14.2.8.1.230, p3372 165-302 CSR

CI = confidence interval; LS = least squares; mITT = modified intention-to-treat; MMRM = mixed-model repeated measures; Phe = phenylalanine; SD = standard deviation

It was unclear why there were missing data from the responder analysis

*Baseline measured from start of PRISM-2 Part 2, defined as the last available blood Phe collected prior to dosing on day 1 of Part 2 (PRISM-2 CSR p 175)

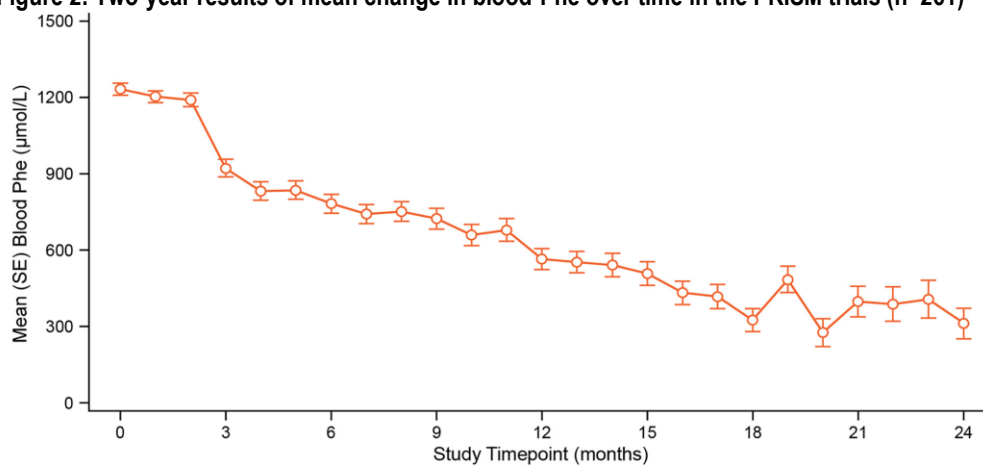
~Based on the mixed model repeated measures (MMRM) method, with study drug (pegvaliase, placebo), visit, and study drug-by-visit interaction as factors adjusting for baseline blood Phe concentration.

[^] Placebo groups separated as results from a mixed model repeated measures analysis of change in blood-Phe concentration from baseline to week 8 reported a P value >0.1, suggesting the groups were different due to carryover effect from different dosage of pegvaliase used in PRISM 2 Part 1.

6.25 In PRISM 1, both pegvaliase 20 mg/day and 40 mg/day led to substantial decreases (mean decrease >350 µmol/L by week 36) in blood-Phe from baseline. However, in the randomised double-blind PRISM 2 Part 2, mean blood-Phe levels actually increased over the eight weeks in patients treated with pegvaliase. This was inconsistent with the assumptions applied in the economic model, discussed in paragraph 6.63, however the PBAC noted that for patients continuing pegvaliase the increase was relatively small and blood-Phe levels remained fairly stable, compared with placebo, where blood-Phe increased substantially. The difference in change from baseline blood-Phe as measured by least squares mean between pegvaliase and placebo was statistically significantly in favour of pegvaliase. Further, more than half (25/49, 51%) of the patients treated with pegvaliase (who were included in the analysis) reported a blood-Phe ≤360 µmol/L. The PBAC noted that there was likely to have been considerable attrition in PRISM 1, with less than a third of patients (80/261) having Phe-level data available at 36 weeks. The PBAC considered that the treatment effect may be overestimated due to the drop out of patients with poor response to pegvaliase.

6.26 The change in blood-Phe for up to two years in patients treated with pegvaliase in PRISM 1/PRISM 2 is presented in Figure 2, and the change in blood-Phe in patients aged ≥ 18 years treated with diet only enrolled in PKUDOS ('previous' patients) is presented in Figure 3.

Figure 2: Two-year results of mean change in blood-Phe over time in the PRISM trials (n=261)



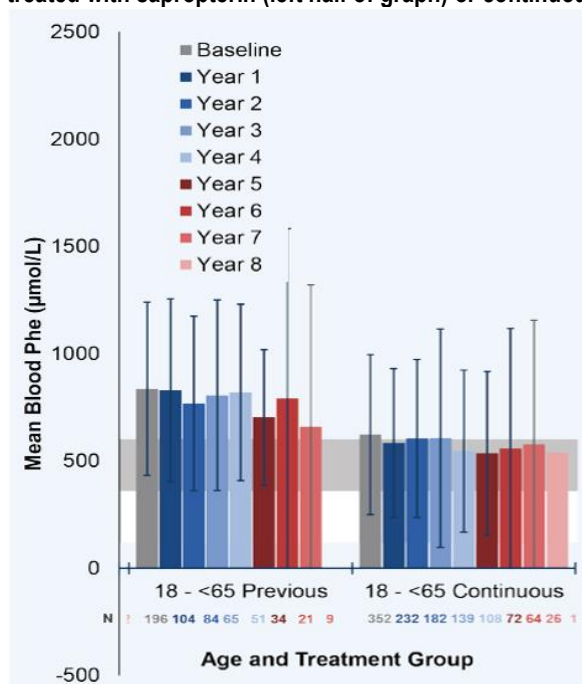
Participants (n): 261

Source: Figure 2.5-7 (p116) of the submission

Phe = phenylalanine; SE = standard error

Sample size reflects patients with data available at study timepoint and who have reached study timepoint at data cut; study is ongoing.

Figure 3: Mean blood-Phe levels over 8 years in PKUDOS in Phe-restricted diet patients who were: previously treated with sapropterin (left half of graph) or continuously treated with sapropterin (right half of graph)



Source: Figure 2.8-9 (p224) of the submission

Phe = phenylalanine; SD = standard deviation

Note: 'Previous' refers to patients who were previously treated with sapropterin but have ceased and managed only with Phe-restricted diet; 'Continuous' refers to currently treated with sapropterin; Light shaded area represents blood-Phe range 120-360 µmol/L; Dark shaded area represents blood-Phe range 360-600 µmol/L.

6.27 Patients treated with pegvaliase in PRISM 1/PRISM 2 reported a slow decline in mean blood-Phe over time which appeared to plateau at around 360 µmol/L by 15-18 months. The sharp decrease in blood-Phe just prior to month 3 appears to approximately align with the minimum time point in the PRISM 1 trial dosing regimen (10 weeks) that allowed patients to titrate up to a dose of 20 mg/day. For reference, patients were kept on a 2.5 mg/week dose for the first 4 weeks of PRISM 1, which is consistent with PI dosing. It is unclear whether this adequately explains the sharp decrease in blood-Phe at this time point. The PBAC noted that although the blood-Phe decreased over time for patients treated with pegvaliase, the number of patients for whom there were data available decreased considerably, with an attrition rate of 80% over 24 months, as shown in Figure 2. The PBAC considered that part of the apparent decline in blood-Phe may be attributable to a selection bias caused by disproportionate drop-out of those with persistently high blood-Phe, rather than therapy.

6.28 The results for the previously treated group in PKUDOS show a slight decrease in blood-Phe over time, however SDs around the estimate are large and over-lapping, and therefore there is a large amount of uncertainty in the results.

Matched-adjusted analysis (Zori et al, 2019)

6.29 The submission presented an unanchored matched-adjusted historical cohort analysis (a sponsor-conducted analysis, Zori et al, 2019), which used propensity score-matching with the following variables: baseline age, gender, and baseline blood Phe concentration. The analysis only included patients who had baseline blood-Phe of ≥ 600 $\mu\text{mol/L}$ and were ≥ 18 years old. The results are presented in Table 6.

Table 6: Blood-Phe level outcome results over time in the Zori et al matched analysis

Proportion of patients, n (%)	Pegvaliase	Phe-restricted diet alone
Year 1	N = 87	N = 51
Blood-Phe $\mu\text{mol/L}$ (mean (SD)) ‡	473 (451)	1022 (322)
By Phe levels (Proportion of patients, n (%))		
≤ 600 $\mu\text{mol/L}$	52 (60)	3 (6)
≤ 360 $\mu\text{mol/L}$	41 (47)	0
≤ 120 $\mu\text{mol/L}$	34 (39)	0
By percentage of Phe reduction (Proportion of patients, n (%))		
$\geq 20\%$ reduction in blood Phe	62 (71)	13 (26)
$\geq 30\%$ reduction in blood Phe	58 (67)	9 (18)
$\geq 50\%$ reduction in blood Phe	50 (58)	0
Year 2	N = 80	N = 42
Blood-Phe $\mu\text{mol/L}$ (mean (SD))	302 (392)	965 (359)
By Phe levels (Proportion of patients, n (%))		
≤ 600 $\mu\text{mol/L}$	63 (79)	5 (12)
≤ 360 $\mu\text{mol/L}$	58 (72)	1 (2)
≤ 120 $\mu\text{mol/L}$	37 (46)	0
By percentage of Phe reduction (Proportion of patients, n (%))		
$\geq 20\%$ reduction in blood Phe	68 (85)	13 (31)
$\geq 30\%$ reduction in blood Phe	65 (81)	9 (21)
$\geq 50\%$ reduction in blood Phe	59 (74)	3 (7)

Source: Table 2.6-3 (p141) of the submission

Phe = phenylalanine; SD = standard deviation

‡ The baseline mean blood-Phe levels between arms in the analysis were comparable. Mean (SD) baseline blood-Phe concentration for patients included in Year 1 analysis: Pegvaliase 1089 (289) $\mu\text{mol/L}$; Phe-restricted diet alone 1037 (271) $\mu\text{mol/L}$

Mean (SD) baseline blood-Phe concentration for patients included in Year 2 analysis: Pegvaliase 1107 (293) $\mu\text{mol/L}$; Phe-restricted diet alone 1051 (302) $\mu\text{mol/L}$

6.30 Zori 2019 reported that matched patients treated with pegvaliase achieved better results across all blood-Phe outcomes than patients treated with Phe-restricted diet. However, the evaluation and the ESC noted the following issues with the analysis:

- Whilst 125 patients per arm were matched at baseline for the analysis, follow-up data were only available for 87 and 51 patients in year 1 for pegvaliase and Phe-restricted diet patients respectively, and 80 and 42 patients respectively in Year 2. It was unclear whether there were systematic differences between these arms in patients due to factors leading to lost to follow up;
- There was no common comparator arm, and as such there was high potential for confounding due to differences in prognostic factors (that were not accounted for in the matching) across single arms of different studies;

- It was unclear whether all relevant effect modifiers and prognostic variables were identified in the analysis. For example, patients were not matched for sapropterin responsiveness, which was also a potential applicability issue;
- The mean blood-Phe levels have large SDs, with the SD around the pegvaliase estimates being larger than the estimated mean blood-Phe. This suggests a sizeable amount of uncertainty with the results; and
- There are no measures of uncertainty around the proportion of patients achieving the blood-Phe outcomes nor any formal statistical testing to allow an estimation of the incremental benefit of pegvaliase compared to diet alone.

6.31 Zori 2019 also presented results comparing matched patients (by age, gender and baseline blood-Phe) treated with pegvaliase (n=43) compared to patients treated with sapropterin plus diet in PKUDOS (n=25). Both treatments led to decreases in blood-Phe over time, but compared to sapropterin, a higher proportion of patients treated with pegvaliase achieved $\leq 360 \mu\text{mol/L}$ at year 1 (2/25 (8%) and 22/43 (51%, respectively) and at year 2 (2/25 (8%) and 26/40 (65%), respectively), suggesting that pegvaliase was more effective than sapropterin at lowering blood-Phe levels.

Naïve indirect comparison

6.32 Rather than using the results of Zori 2019 to inform the economic evaluation, the economic model relied on pegvaliase responder rates from the naïve indirect comparison. The results from the naïve indirect comparison are presented in Table 7.

Table 7: Blood-Phe level outcome results over time in the indirect comparison

Time period	$\leq 360 \mu\text{mol/L}$			$\geq 30\%$ reduction from baseline		
	Pegvaliase n (%)	Phe-restricted diet n (%)	OR (95% CI) ‡	Pegvaliase n (%)	Phe-restricted diet n (%)	OR (95% CI) ‡
Baseline	n = 261 0 (0%)	n = 50 0 (0%)	-	n = 261 0 (0%)	n = 50 0 (0%)	-
1-6 months	n = 257 70 (27%)	n = 37 6 (16%)	0.52 (0.21, 1.29)	n = 257 145 (56%)	n = 37 11 (30%)	0.33 (0.15, 0.69)
7-12 months	n = 209 96 (46%)	n = 32 4 (13%)	0.19 (0.06, 0.50)	n = 209 147 (70%)	n = 32 9 (28%)	0.17 (0.07, 0.38)
Year 2	n = 186 ^ 135 (73%)	n = 27 3 (11%)	0.06 (0.01, 0.16)	n = 186 169 (91%)	n = 27 13 (48%)	0.09 (0.04, 0.23)
Year 2 ±	n = 261 135 (52%)	n = 50 3 (6%)	0.06 (0.01, 0.19)	n = 261 169 (65%)	n = 50 13 (26%)	0.19 (0.10, 0.38)
Year 3	n = 162 139 (86%)	n = 21 2 (10%)	0.02 (0.00, 0.08)	n = 162 152 (94%)	n = 21 7 (33%)	0.03 (0.01, 0.10)
Year 4	n = 132 112 (85%)	n = 13 2 (15%)	0.04 (0.01, 0.18)	n = 132 124 (94%)	n = 13 6 (46%)	0.06 (0.02, 0.20)
Year 5	n = 74 58 (78%)	n = 11 0 (0%)	0.01 (0.00, 0.22)	n = 74 69 (93%)	n = 11 2 (18%)	0.20 (0.00, 0.01)

Source: Table 2.6-7 to 9 (p153-5) of the submission; evaluator-conducted calculations

CI = confidence interval; OR = Odds ratio; Phe = phenylalanine

‡ Bold denotes a statistically significant value ($p \leq 0.05$)

^ 21 patients were further excluded from the economic evaluation (n=165), as it was stated that they did not remain on pegvaliase for two years, and a response rate of 81.8% (135/165) was used in the economic evaluation.

± Grey-shading denotes evaluator-conducted analysis using total baseline sample size in denominator

- 6.33 The proportion of pegvaliase responders (achieving blood-Phe $\leq 360 \mu\text{mol/L}$) was calculated based on the number of patients ‘at risk’ at a particular time point (i.e., using an observed case basis) rather than all patients enrolled (i.e., the full analysis set). This biased the results in favour of pegvaliase because patients who discontinue treatment were effectively not considered to be non-responders and simply censored. During the evaluation, the proportion of responders at two years (timepoint used in the economic evaluation and aligns with the proposed restriction for response assessment) was calculated using all patients enrolled at baseline, and the proportion of responders in pegvaliase decreased from 73% (135/186) to 52% (135/261).
- 6.34 In the economic evaluation, only data from patients who remained on pegvaliase treatment for two years were included for the assessment of the proportion of pegvaliase responders. This resulted in 21 patients being excluded from the analysis compared to the total number of patients still being followed at year 2 reported in Table 7, and an 81.8% (135/165) blood-Phe response rate was assumed for pegvaliase. The PSCR argued that pegvaliase discontinuations were modelled separately in the economic analysis, such that pegvaliase overall response at 2 years was approximately 61% (which also included additional patients who responded based on ADHD-RS).
- 6.35 Comparatively, a 0% response rate was assumed in the economic model for Phe-restricted diet only patients, which was not supported by the data which reported up to 16% blood-Phe response rate at 6 months (using the submission’s calculation methods). This favoured pegvaliase in the economic model.

ADHD-RS inattention scale

- 6.36 The results for change in ADHD-RS inattention subscale scores over time in patients treated with pegvaliase in PRISM 1 as well as the comparative results from PRISM 2 Part 2 are presented below.

Table 8: Results of change in ADHD RS-IV inattention subscale over 26-36 weeks in PRISM 1

	Pegvaliase 20 mg/day	Pegvaliase 40 mg/day
ADHD RS-IV IA subscore	N = 131	N = 130
Baseline	n = 129	n = 124
Mean (SD)	10.0 (6.6)	9.5 (5.6)
Median (min, max)	9.0 (0.0, 26.0)	8.0 (0.0, 23.0)
End of study	n = 96	n = 93
Mean (SD)	6.2 (5.2)	6.9 (5.0)
Median (min, max)	5.0 (0.0, 24.0)	6.0 (0.0, 20.0)
Change from baseline to end of study*	n = 94	n = 87
Mean (SD)	-3.7 (5.2)	-3.2 (5.3)
Median (min, max)	-3.0 (-23.0, 10.0)	-2.0 (-18.0, 10.0)

Source: Table 2.5-3 (p102) of the submission

ADHD RS-IV IA = Attention Deficit Hyperactivity Disorder Rating Scale Inattention subscale; PKU = phenylketonuria; POMS = Profile of Mood States; SD = standard deviation; TMD = total mood disturbance

* Based on patients with available measurements at both time points

Table 9: Results of change in ADHD RS-IV inattention subscale from PRISM 2 Part 2 baseline to week 8

	Pooled pegvaliase N = 58	Placebo 20 mg/day N = 14	Placebo 40 mg/day N = 14

Public Summary Document – July 2022 PBAC Meeting

ADHD RS-IV IA subscale score			
N	58	14	14
Baseline*, mean (SD)	5.9 (5.54)	5.0 (4.26)	2.9 (3.68)
Week 8, mean (SD)	6.8 (5.98)	6.0 (4.58)	3.2 (2.86)
Change from baseline			
Mean (SD)	0.8 (4.62)	1.2 (3.00)	-0.4 (3.44)
LS mean (95% CI)	1.24 (0.03, 2.45)	0.74 (-1.52, 3.01)	-0.40 (-2.93, 2.12)
Pooled active vs placebo			
Difference in LS means (95% CI)	-	0.50 (-2.07, 3.06); p = 0.707	1.64 (-1.16, 4.45); p = 0.2469
ADHD RS-IV IA subscale score in PRISM-1 patients with baseline [^] score > 9			
N	26	5	6
Baseline*, mean (SD)	7.5 (5.29)	8.0 (3.94)	4.7 (4.50)
Week 8, mean (SD)	9.9 (4.97)	7.8 (3.69)	5.5 (2.65)
Change from baseline			
Mean (SD)	2.5 (4.69)	-0.5 (2.52)	-1.0 (3.56)
LS mean (95% CI)	3.05 (1.10, 5.00)	-1.62 (-6.07, 2.83)	0.28 (-4.05, 4.61)
Pooled active vs placebo			
Difference in LS means (95% CI)	-	4.67 (-0.19, 9.53); p = 0.0591	2.77 (-1.99, 7.52); p = 0.2447

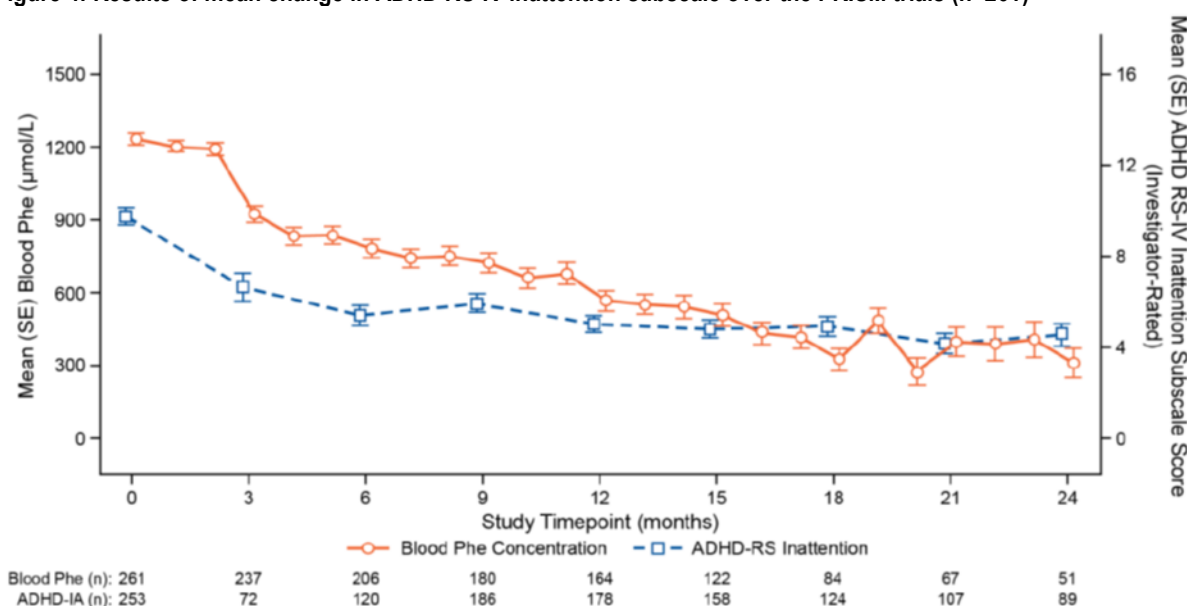
Source: Table 2.5-7 (p112) of the submission

ADHD RS-IV IA = Attention Deficit Hyperactivity Disorder Rating Scale IV Inattention subscale; CI = confidence interval; mITT = modified intention-to-treat; LS = least squares; POMS = Profile of Mood States; PKU = phenylketonuria; SD = standard deviation; TMD = total mood disturbance

*Refers to baseline at the start of PRISM-2 Part 2

[^] Refers to pegvaliase-naïve baseline

Figure 4: Results of mean change in ADHD RS-IV inattention subscale over the PRISM trials (n=261)



Source: Figure 2.5-9 (p118) of the submission

ADHD RS-IV IA = Attention Deficit Hyperactivity Disorder Rating Scale IV Inattention subscale; Phe = phenylalanine; SE = standard error

6.37 In PRISM 1, both the pegvaliase 20 mg/day and 40 mg/day groups in both the total trial population and the subgroup of patients with ADHD RS-IV inattention score >9 at baseline had lower inattention subscale scores at the end of the study than at baseline

indicating an improvement in symptoms. However, the standard deviations around these mean changes are larger than the mean change themselves, indicating a high degree of uncertainty. Additionally, it was unclear if these score changes were clinically meaningful as the mean and median change were below the MCID (≥ 5 point change from baseline) nominated in the submission.

- 6.38 In the total PRISM 2 Part 2 population, the pooled pegvaliase and placebo 20 mg/day arms had minor increases over 8 weeks in inattention subscale scores whereas the placebo 40 mg/day arm had a minor decrease. The results for patients with a pegvaliase-naïve baseline ADHD-RS inattention subscale score >9 shows pooled pegvaliase patients increased in inattention subscale scores over the 8 weeks of PRISM 2 Part 2 (by 2.5) whilst both placebo arms decreased in scores. These results do not appear to support the claim of clinical efficacy in terms of improvement in ADHD-RS inattention subscale scores with treatment with pegvaliase and further do not support the correlation between blood-Phe and ADHD inattention subscale scores as assumed by the submission in the economic model (see paragraph 6.63).
- 6.39 The submission claimed that, among the 30 patients treated with pegvaliase who did not achieve a blood-Phe of ≤ 360 $\mu\text{mol/L}$ in PRISM 1 and PRISM 2 (see paragraph 6.34), 14 patients achieved a reduction of ≥ 5 points in the ADHD-RS inattention subscale score, and therefore an 8.5% (14/165) response rate for ADHD-RS was assumed in the economic model. Inappropriately, no response rate data for patients treated with Phe-restricted diet was presented, and as such it was not possible to assess the incremental benefit of pegvaliase for this outcome. The submission assumed no patient treated with Phe-restricted diet could achieved a reduction of ≥ 5 points in the ADHD-RS inattention subscale score in the economic model.

PRISM subgroup results by sapropterin responder status

- 6.40 The results of a subgroup analysis of PRISM trial data by sapropterin ‘responders’ vs ‘non-responders’ are presented below. Sapropterin responders were defined as patients who had > 4 week consecutive sapropterin treatment within 6 months of their screening visit and had exhibited a clinically significant decrease in blood Phe levels per investigator determination. While this does not align with the PBS criteria for sapropterin response (which is a $\geq 30\%$ reduction in 7 days), the analysis is informative in determining the appropriateness of restricting use of pegvaliase to sapropterin non-responders.

Table 10: Blood-Phe levels over time by sapropterin responder status in the PRISM trials

Blood Phe Concentration (µmol/L)	Sapropterin non-responder (N = 144)	Sapropterin responder [^] (N = 52)
Baseline		
n	144	52
Mean (SD)	1278.1 (377.2)	1131.8 (363.7)
Median (min, max)	1281.5 (483, 2330)	1045.0 (568, 1889)
12 months		
n	93	34
Mean (SD)	502.5 (530.7)	692.3 (519.2)
Median (min, max)	338.0 (0, 2001)	687.5 (0, 1816)
24 months		
n	59	12
Mean (SD)	335.5 (456.25)	349.0 (436.44)
Median (min, max)	120.0 (0, 1640)	165.0 (0, 1374)
36 months		
n	24	8
Mean (SD)	335.6 (458.4)	294.4 (315.6)
Median	54.5 (0, 1647)	173.0 (32, 983)

Source: Table 2.6-1 (p136) of the submission

[^] defined as patient who had >4 week consecutive sapropterin treatment within 6 months of screening visit and had exhibited a clinically significant decrease in blood Phe levels per investigator determination

SD = standard deviation

6.41 The submission considered the results of the subgroup analysis demonstrates a similar treatment effect of pegvaliase in sapropterin responders and non-responders which therefore justifies the use of the ITT population to indicate efficacy in the sapropterin non-responder population. The evaluation and the ESC considered that the results of this analysis were highly uncertain as no statistical tests were conducted to support the claim of no difference, there were very small sample sizes at later time points and the SDs around the means at baseline are wide. However, assuming the submission’s analysis was accurate, then it may be inequitable to restrict pegvaliase to sapropterin non-responders. The PBAC considered that if there is a similar treatment effect of pegvaliase in responders and non-responders, restricting pegvaliase to sapropterin non-responders does not identify a group more likely to respond to treatment and therefore the approach is not clinically justified.

Literature review: relationship between blood-Phe and neuropsychiatric symptoms in adults

6.42 Based on a literature review (presented as an appendix), the submission claimed that a lower blood-Phe was correlated with fewer neuropsychiatric symptoms in adults. Overall, while it was biologically plausible that a lower blood-Phe was correlated with fewer neuropsychiatric symptoms in adults, the evaluation and the ESC considered that the exact correlation was uncertain, and the incremental benefit associated with treatment with sapropterin or pegvaliase was difficult to accurately quantify. The published regression models in Bilder 2016 and Burgess 2021 did not report any statistically significant correlations between Phe and neuropsychiatric outcomes. Further, PKU-016 also reported no statistically significant differences between adults with PKU treated with sapropterin or placebo in ADHD-RS and BRIEF scores.

- 6.43 The submission also claimed that a relationship between increases in Phe tolerance and increased quality of life was supported by the time burden studies and HRQoL evidence. This was plausible and reasonable and was captured in the time trade off (TTO) study used in the economic model (see Table 14 below). However, differences in dietary Phe were not considered in the clinical claim or economic model. In reality, it is likely some adult patients who achieve a response to pegvaliase would choose to trade-off some of the blood-Phe lowering effects with pegvaliase by relaxing their Phe-restricted diet. For example, in the PRISM studies, patients treated with pegvaliase 20mg/day had minor increases in daily protein intake and daily Phe intake over time, whereas those treated with pegvaliase 40mg/day had larger increases in daily protein and Phe intake over time. However, overall, the extent of this could not be elicited from the available data. For reference, the TTO study conducted by the sponsor estimated the disutility associated with: a restricted diet with medical food to be 0.173; and a partly restricted diet without medical food to be 0.062, assuming no change in PKU symptoms. The ESC considered that normalisation of diet may be an important treatment goal. However, the ESC also considered that this may result in limited applicability of the clinical trial outcomes for pegvaliase to clinical practice.

Comparative harms

- 6.44 The safety results for patients treated with pegvaliase and placebo from PRISM 2 Part 2 are presented below.

Table 11: Summary of AEs in PRISM 2 Part 2

Adverse event type, n (%)	Incidence		Risk Difference (95% CI)
	Pooled pegvaliase (N = 66)	Pooled placebo (N = 29)	
Duration of exposure, days, mean (SD)	54.4 (6.91)	55.0 (5.21)	
Duration of exposure (person-years)	9.8	4.4 ‡	
Deaths	0	0	0
AEs			
Any AEs	55 (83.3)	27 (93.1)	-0.10 (-0.23, 0.03)
Drug-related AEs	44 (66.7)	16 (55.2)	0.12 (-0.10, 0.33)
AEs causing dose interruption or reduction	1 (1.5)	1 (3.4)	-0.02 (-0.09, 0.05)
SAEs			
Any SAEs †	2 (3.0)	1 (3.4)	-0.00 (-0.08, 0.07)
Drug-related SAEs	2 (3.0)	0	0.03 (-0.01, 0.07)
Adverse events of Special Interest			
Anaphylaxis (per NIAID/ FAAN Criteria)	0	0	0
Anaphylaxis (per Brown's severe criteria)	0	0	0
Adverse events of Significance			
Hypersensitivity AEs	26 (39.4)	4 (13.8)	0.26 (0.08, 0.43)
Generalised skin reaction ≥ 14 days	7 (10.6)	0	0.11 (0.03, 0.19)
Injection-site skin reaction ≥ 14 days	5 (7.6)	1 (3.4)	0.04 (-0.05, 0.13)
Arthralgia	9 (13.6)	3 (10.3)	0.03 (-0.10, 0.17)
Injection-site reaction	16 (24.2)	7 (24.1)	0.00 (-0.19, 0.19)

Source: Table 2.5-14 (p125-6) of the submission; Evaluator-compiled Risk Differences

AE = adverse event; AESI = adverse event of special interest; CI = confidence interval; FAAN = food allergy and anaphylaxis network; NIAID = National Institute of Allergy and Infectious Diseases; SAE = serious adverse event; SD = standard deviation

‡ Patients in Part 2 placebo group received 4.4 person-years of exposure to placebo

† Additional AEs (8 events for 4 patients) were upgraded by the sponsor to SAEs and were not factored into the incidence or event rates of the summary tables

- 6.45 The results from PRISM 2 Part 2 indicate that patients treated with pegvaliase had a higher incidence of hypersensitivity (RD = 0.26, 95%CI 0.09, 0.43) and generalised skin reactions lasting longer than 14 days (RD = 0.11, 95%CI 0.03, 0.19). Although injection site reactions were not statistically different between treatments in PRISM 2 Part 2, in clinical practice, patients would not receive placebo injections therefore it is also expected that injection site reactions would be more frequent with pegvaliase compared to patients on Phe-restricted diets alone. PRISM 2 Part 2 only treated patients for eight weeks, therefore the comparative safety over a longer treatment period was unknown.
- 6.46 The anaphylaxis results in the table above are based on PRISM 2 Part 2, in which patients had already been exposed to pegvaliase for an extended period. The Delegate's Overview states that pegvaliase is 'highly immunogenic. Hypersensitivity reactions were very common, most of these were mild- moderate. Anaphylaxis or acute hypersensitivity occurred in around 20%' and that 'the risk mitigation strategy proposed [to the TGA] was included as a protocol amendment to the clinical studies in May 2014. This included premedication with a H1, H2 antagonist and NSAID; having a trained observer present at the time of injections; training in the recognition and treatment of hypersensitivity; use of an EpiPen; and an extension of the initiation and titration phase from 14 weeks to 26 weeks.' The PBAC noted that patients who

discontinued pegvaliase due to intolerance of therapy in PRISM 1 or PRISM 2 Part 1 were not included in PRISM 2 Part 2 and therefore the AE rates in Table 11, particularly hypersensitivity AE and generalised skin reaction, are likely to underestimate the true burden of AEs for pegvaliase.

Benefits/harms

6.47 A summary of the comparative benefits and harms for pegvaliase versus placebo (as a proxy for Phe-restricted diet alone) is presented below.

Table 12. Summary of comparative benefits for pegvaliase compared to placebo

	Pegvaliase n/N	Placebo n/N	RR (95% CI)	Event rate/100 patients *		RD (95% CI)	
				Pegvaliase	Placebo		
Benefits							
Proportion achieving $\leq 360 \mu\text{mol/L}$							
PRISM 2 Part 2	25/49	0/23	24.5 (3.53, NA)	51	0	0.51 (0.35, 0.65)	
Change from baseline blood Phe levels							
Trial	Pegvaliase			Placebo †			Mean difference Pegvaliase vs. placebo (95% CI)
	N	Mean Δ baseline ($\mu\text{mol/L}$)	SD	N	Mean Δ baseline ($\mu\text{mol/L}$)	SD	
PRISM 2 Part 2	58	18.6	279.43	14	599.0	507.40	-580.4 (382, 779)
Harms							
	Pegvaliase n/N	Placebo n/N	RR (95% CI)	Event rate/100 patients		RD (95% CI)	
				Pegvaliase	Placebo		
Hypersensitivity AEs							
PRISM 2 Part 2	26/66	4/29	2.86 (1.21, 7.45)	39.4	13.8	0.26 (0.08, 0.43)	
Generalised skin reaction ≥ 14 days							
PRISM 2 Part 2	7/66	0/29	6.73 (0.87, NA)	10.6	0	0.11 (0.03, 0.19)	

Source: Compiled during the evaluation

† 40 mg/day placebo group

*8 week trial duration

6.48 On the basis of direct evidence presented by the submission, for every 100 patients treated with pegvaliase plus Phe-restricted diet in comparison with Phe-restricted diet, after eight weeks:

- Approximately 51 additional patients achieve a blood-Phe level of $\leq 360 \mu\text{mol/L}$.

6.49 On the basis of direct evidence presented by the submission, for every 100 patients treated with pegvaliase plus Phe-restricted diet in comparison with a Phe-restricted diet alone:

- Approximately 26 more patients would have a hypersensitivity adverse event; and
- Approximately 11 more patients would have a generalised skin reaction lasting more than 14 days.

6.50 As noted above, the PBAC considered that the true rate of hypersensitivity AEs and generalised skin reactions are likely to be substantially higher than the above values, which were based on PRISM 2 Part 2.

Clinical claim

- 6.51 The submission described pegvaliase plus a Phe-restricted diet as superior in terms of effectiveness compared with a Phe-restricted diet. The PSCR confirmed that the clinical claim was based on the composite outcome of: a blood-Phe < 360 µmol/L; and/or a ≥ 5-point change from baseline in the ADHD-RS inattention subscale score.
- 6.52 The ESC considered that the evidence suggested that pegvaliase may be effective at reducing blood-Phe levels given the difference in the proportion of patients achieving a blood-Phe ≤360 µmol/L with pegvaliase (52-73% at 2 years, depending on denominator) versus a Phe-restricted diet alone (6-11% at 2 years, depending on denominator), based on the matched-adjusted analysis and the naïve-indirect comparison. However, the ESC considered that it was not possible to quantify the magnitude of the incremental benefit based on the evidence provided given the limitations in the methodology of both comparisons and the poor quality of the evidence underpinning these comparisons (e.g., the high risk of bias in the studies and the lack of detailed information about the flow of patients through PKUDOS). The only randomised comparative data were from a short term, 8 week trial with 86 patients (PRISM 2 Part 2) which found that pegvaliase (n=58) was associated with a statistically significant (P<0.0001) higher reduction in mean blood-Phe from baseline, compared with placebo (n=28). Overall, the ESC considered there was a very high level of uncertainty in the clinical evidence and comparative effectiveness estimates, and that the submission had likely overestimated the benefit of pegvaliase (e.g., PRISM 2 Part 2 only included patients who had received pegvaliase for a significant period of time and had achieved ≥ 20% reduction in blood-Phe; and as such included patients who already had a degree of responsiveness to pegvaliase). The pre-PBAC acknowledged the limitations of the data but noted that PKU is a rare disease, which poses challenges to generating high quality clinical evidence and stated that no further substantial evidence for pegvaliase is likely to be forthcoming.
- 6.53 The submission did not provide any comparative data for the proportion of patients who achieved a response defined as a ≥5 point improvement in the ADHD-RS inattention subscale score. Thus, the evaluation and the ESC considered that the claim of superior effectiveness in the ADHD-RS inattention subscale score, and for the composite outcome, was poorly supported and did not support the use of this composite outcome within the requested restrictions or in the economic evaluation (noting this composite outcome would allow more patients to be eligible for ongoing treatment, and to be classed as responders in the economic evaluation). Supportive evidence from the literature suggests that a reduction in blood-Phe is plausibly related to a reduction in neuropsychiatric symptoms though this difference was difficult to quantify and did not reach statistical significance in regression models (Bilder 2016 and Burgess 2021) or in randomised controlled trials (PKU-016). Overall, the magnitude of benefit in the proportion of patients achieving a clinically meaningful (≥ 5 point) improvement in the ADHD-RS inattention subscale score in the requested population, specifically when treated with pegvaliase, was highly uncertain.

- 6.54 The submission described pegvaliase plus a Phe-restricted diet as inferior in terms of safety compared to a Phe-restricted diet. This claim was supported, however given the lack of longer-term comparative data the magnitude of the difference over a longer treatment period was uncertain.
- 6.55 The submission did not make a clinical claim versus sapropterin given it had positioned the two drugs in separate lines of therapy. As outlined in paragraph 6.31, there is some evidence to suggest that pegvaliase may be more effective than sapropterin at lowering blood-Phe. Pegvaliase may have inferior safety to sapropterin given the submission describes pegvaliase as inferior in terms of safety compared to a Phe-restricted diet, while the PBAC has previously accepted that sapropterin has non-inferior safety compared to a Phe-restricted diet in adults (paragraph 7.8, sapropterin PSD, November 2020 PBAC meeting).
- 6.56 The PBAC considered that the claim of superior comparative effectiveness to a Phe-restricted diet alone was reasonable, in terms of blood-Phe reduction.
- 6.57 The PBAC considered that the claim of inferior comparative safety to a Phe-restricted diet alone was reasonable.

Economic analysis

- 6.58 The submission presented a cost-utility analysis using a micro-simulation model. This is consistent with the clinical claim.
- 6.59 The model structure, key inputs and rationale are presented in Table 13.

Table 13: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Pegvaliase plus a Phe-restricted diet vs a Phe-restricted diet alone
Time horizon	Lifetime (up to 100 years of age) in the model base-case vs 5 years in the key clinical studies
Outcomes	Responders and quality adjusted life years gained
Methods used to generate results	Microsimulation model using @Risk and Microsoft Excel
Health states	'Responder', 'non-responder', 'Phe-restricted diet' and 'dead'. Responder defined as achieving either ≤ 360 $\mu\text{mol/L}$ or ADHD-RS inattention subscale reduction of ≥ 5 from baseline by 2 years
Cycle length	1 week
Transition probabilities	<p>Pegvaliase response rate: Calculated from an analysis of February 2019 PRISM trial data-cut of patients with ≥ 2 years of pegvaliase treatment who achieved either ≤ 360 $\mu\text{mol/L}$ (81.8%) or ADHD-RS inattention subscale reduction of ≥ 5 from baseline (8.5%).</p> <p>Phe-diet alone response rate: Assumed to be 0%.</p> <p>Pegvaliase blood-Phe level over time: Estimated using an exponential regression with plateaus at particular time-points (for blood-Phe responders and for non-responders on pegvaliase) and linear regression (for ADHD responders) from the above PRISM data-cut.</p> <p>Phe-diet alone blood-Phe level over time: Estimated from an additional analysis of the PKUDOS registry dataset and applied as a 108 $\mu\text{mol/L}$ reduction from baseline and assumed as constant thereafter.</p> <p>Pegvaliase discontinuation rate: Calculated as time-dependent discontinuation rates up to 5 years from the above PRISM data-cut with no discontinuation from Year 5 onwards.</p> <p>Phe-diet alone discontinuation rate: Assumed to be 0%.</p> <p>Overall survival: Gender and age adjusted general population mortality.</p> <p>Pegvaliase adverse events: Calculated from the incidence of adverse events \geq Grade 3 that occurred in $\geq 1\%$ of patients in PRISM 1 trial.</p> <p>Phe-diet alone adverse events: Assumed to be 0%</p>
Health related quality of life	TTO direct elicitation with Swedish general population preference weights. Utility values for health states from the utility study were applied to blood-Phe categories assumed by the submission to correspond to the given health states.

Source: Table 3.1-1, pp260-1 of the submission

ADHD-RS = Attention Deficit Hyperactivity Disorder Rating Scale; Phe = phenylalanine; TTO = time trade off

- 6.60 Microsimulation is used to determine the gender (which affects background mortality based on Australian life tables), baseline Phe, age at treatment initiation and death, responder status and time of pegvaliase discontinuation. Only patients treated with pegvaliase can respond in the model. Phe-restricted diet patients remain in a Phe-restricted diet health state until death.
- 6.61 The ESC considered that there was a lack of clinical data available to support the microsimulation approach undertaken. While the submission claimed that a microsimulation approach was justified as blood-Phe levels and quality of life are continuous variables, transitions in blood-Phe level could have been modelled using a cohort model (as was presented for previous sapropterin submissions in PKU), and quality of life was derived from mapping categorical variables based on time trade off results to assumed blood Phe levels. The use of a microsimulation model resulted in unnecessarily complicated model, which required significant time to compute. For this

reason, only limited sensitivity analyses could be conducted during the evaluation, mostly using only 100 iterations.

- 6.62 The PSCR reiterated that a Markov model would be problematic in this circumstance as the health states are based on the continuous outcome of blood Phe for which there are no established thresholds at which a sudden marked change in functioning and quality of life are observed. The PSCR argued that reductions in blood Phe levels over time result in gradual but continuous improvements in functioning and quality of life. The PSCR and pre-PBAC response claimed that a large number of health states would be required to prevent disproportionate changes in QoL, which may be computationally more complex than the use of regression equations and there would be a lack of data to inform all the health state transitions. However, the ESC considered this justification was inadequate as: there were a corresponding lack of data to inform the microsimulation approach undertaken; and as outlined above, the utility values were derived from blood-Phe level categories (akin to ‘mapped health states’).
- 6.63 Pegvaliase patients who respond in the model can respond either by achieving a blood-Phe $<360 \mu\text{mol/L}$ or an ADHD-RS inattention subscale score change ≥ 5 from baseline (response rates of 90.3% in the pegvaliase arm, and 0% in the Phe-diet alone arm were used). Non-responders remain on treatment until 2 years in the model then switch to a Phe-restricted diet.
- 6.64 Pegvaliase patients are assumed to experience a decrease in blood-Phe each cycle they remain on treatment (based on equations that differ based on type of response) until they reach a plateau of $261 \mu\text{mol/L}$, unless they discontinue treatment and transition to a Phe-restricted diet. Patients treated with Phe-restricted diet only were assigned a once off improvement in blood-Phe of $108 \mu\text{mol/L}$ at the first cycle.
- 6.65 In the pegvaliase arm of the model, the equations for estimating blood-Phe levels each cycle were based on the same data as were used to inform the naïve indirect comparison. As such, the ESC noted the economic evaluation was subject to the limitations of this data including the high risk of bias of the included studies. To derive the equation for pegvaliase Phe $\leq 360 \mu\text{mol/L}$ responders, the submission applied a non-linear exponential regression with asymptote. Only limited goodness of fit statistics were presented to justify the appropriateness of the regression equation, and the evaluation considered that it was unlikely that a univariate extrapolation was appropriate as other factors like age and daily dietary Phe would impact blood-Phe. The wide variance in data points in the fitted plot make it difficult to visually assess whether the fitted curve is a reasonable fit to the data. Overall, the ESC considered there was limited testing for goodness of fit and a large amount of variance in the underpinning data.
- 6.66 As discussed in paragraph 6.25, a number of patients who achieved at least one reading of blood-Phe $\leq 360 \mu\text{mol/L}$ within the first two years subsequently reported

higher blood-Phe levels, which was inconsistent with the model's assumption that all patients who were responders will maintain a reduced blood-Phe over time.

- 6.67 The model also assumed that Phe-restricted diet patients were unable to achieve a response, which contradicts the clinical evidence presented in the indirect naïve comparison (see Table 7). The PSCR argued that this was appropriate as the requested population comprises patients who have inadequate blood-Phe control despite prior management with sapropterin and a Phe restricted diet alone. However, the data in Table 7 informing the Phe-restricted diet arm (from the PKUDOS registry) comprises patients who had discontinued sapropterin (reasons for discontinuation were unknown). While not directly applicable to the requested population, this indicates that some Phe-restricted diet patients who have decided to cease sapropterin can achieve a response.
- 6.68 The utility values used in the submission were based on a sponsor commissioned utility study which included a time trade off (TTO) (n=1,106) and discrete choice experiment (DCE) (n=1,117) component, from a mix of PKU experienced people (n=17) and adults from the general Swedish population. Utility values for discrete health states (no symptoms, mild, moderate or severe symptoms, and no diet or partial diet restrictions) from the utility study were correlated to blood-Phe categories assumed by the submission to correspond to the given health states. The results from the sponsor-commissioned utility study, and the utility changes for each 1 µmol/L change in blood Phe applied in the model (which was dependent on the blood-Phe range), are presented in Table 14.

Table 14. Utility value results from sponsor commissioned utility study and as applied in economic model

Health State [‡]	TTO mean utility (SD) [N / median]	Blood-Phe level category applied in the economic model [*] Reference blood-Phe (utility)	Change in utility for each 1 µmol/L change applied in model
No diet restrictions and no symptoms	0.837 (0.259) [425 / 0.950]	<120 µmol/L [‡]	0 [^]
Partly-restricted diet without medical food and no symptoms	0.775 (0.302) [411 / 0.900]	120 – 360 µmol/L 240 µmol/L(0.775)	120- 240: 0.00051 241-360: 0.00046
No symptoms and restricted diet with medical food	0.664 (0.412) [409 / 0.825]	360 – 600 µmol/L 480 µmol/L(0.664)	361-480: 0.00046 481-600: 0.00017
Mild symptoms and restricted diet with medical food	0.591 (0.450) [415 / 0.725]	600 – 1,200 µmol/L 900 µmol/L(0.591)	601-900: 0.00017 ≥901: 0.00090
Moderate symptoms and restricted diet with medical food	0.504 (0.437) [399 / 0.600]	Mean utility value of these two health states applied to ≥1,201 µmol/L 1,201 µmol/L(0.321)	
Severe symptoms and restricted diet with medical food	0.138 (0.570) [39 / 0.275]		

Source: Tables 3 and 4.2 in Appendix 18 of the submission, Palyzniq (pegvaliase) – Kuvan (sapropterin) – CEA.xlsx

Phe = phenylalanine; SD = standard deviation; TTO = time trade-off

[^] All patients with Phe 0-119 µmol/L assumed to have maximum utility of 0.837

[‡] ‘Symptoms’ were described in health state vignettes for emotional, cognitive and physical symptoms.

^{*} Patients were not assigned blood-Phe values <261 µmol/L in the economic model, however the submission applied TTO health state utility values to blood-Phe categories and used linear interpolation between these to derive utility values by blood-Phe level in the model. As such, the submission used <120 µmol/L as a blood-Phe category to inform the interpolation.

[‡] The submission applied the utility value to the mid-point blood-Phe value for the category in order to derive utility values by blood-Phe using linear interpolation

- 6.69 The evaluation and the ESC considered that it was unclear if the health states from the TTO study adequately aligned with the specific Phe values used in the model given the lack of clinical data to support this assumption. It was also unreasonable to assume that a change of just 1 µmol/L in blood-Phe level would lead to a change in patient utility, nor was it reasonable to assume that changes of utility less than 0.001 were clinically relevant or that the utility instruments used to derive the utilities were sensitive enough to have detected such changes. The PSCR reiterated that changes in blood-Phe levels over time are associated with gradual but continuous improvements in quality of life, which become meaningful when accumulated over time.
- 6.70 The submission claimed that the utilities applied in the current analysis are broadly consistent with those used in previous submissions to the PBAC for sapropterin (i.e., sapropterin: 0.71; Phe restricted diet only: 0.59; relaxed Phe restricted diet: 0.48 and uncontrolled: 0.37). However, the lower end utilities applied in the current submission were less conservative than those applied in the March 2018 sapropterin submission. For example, a Phe-restricted diet patient with a simulated baseline blood-Phe >1,201 µmol/L would receive a utility value of 0.321, whereas uncontrolled blood Phe was assigned a utility of 0.37 in March 2018. Moreover, given the established developmental effects of uncontrolled Phe levels in paediatric PKU patients, and the fact that these effects have either occurred or not in adulthood and will thus not be affected by adult Phe levels, it was unclear why the utility values in the adult population should be consistent with the previous considerations which included children and adolescents. The PBAC has previously considered that “it is highly likely that potential health impacts of uncontrolled PKU are more severe in infants and

Public Summary Document – July 2022 PBAC Meeting

young children than in adults” (paragraph 6.49, sapropterin PSD, March 2018 PBAC meeting) and as such, it would be expected that the utility of uncontrolled PKU in adults should be higher relative to children and adolescents, whereas the opposite is true in the current submission. This likely meant that the utility of uncontrolled PKU was underestimated in the current submission, which favours pegvaliase.

6.71 The PBAC noted that utility values applied in the submission were less conservative than in the March 2018 sapropterin submission, however the PBAC also noted that consumer input emphasised the high disutility experienced by patients both for severe symptoms and from highly restricted diet and the requirement for food supplements.

6.72 Key drivers of the model are presented in Table 15.

Table 15: Key drivers of the model

Description	Method/Value	Impact Base case: \$11/QALY
Dosage of pegvaliase	Maintenance dose assumed to be 30.5 mg/day in base case based on relative treatment days at each dosage in PRISM 1 and PRISM 2. However, this included treatment days in titration period and was based on the use of only average treatment days for up to five years, which underestimates the long term average dose. For example, at five years of follow up, a patient who slowly titrated up to 60 mg/kg over two years would only have spent 60% (three out of five years) of their treatment days on the 60 mg/kg dose. However, at 20 years follow up, assuming they remained on 60 mg/kg, this percentage would instead be 90% (18 out of 20 years). 11.9% of treatment days were at 0 mg/day usage.	High. Assuming a maintenance dose of 60 mg/day increased the ICER to \$██████████ ² , an increase of 84%.
Baseline Phe	The distribution of baseline Phe from patients enrolled in PRISM 1 and PRISM 2 was used to inform the microsimulation. However, the results could vary significantly, with the lognormal distribution around a mean of 1,215 µmol/L having a 5% value of 710 µmol/L and 95% value of 1,884 µmol/L	Probabilistic sensitivity analysis showed that baseline blood-Phe has a negative correlation with the ICER, with a lower baseline blood-Phe leading to a higher ICER. Assuming a baseline blood-Phe of 953.93 µmol/L (25 th percentile of distribution) increased the ICER by 84%
Utility assumption	Based on mapping from TTO with a higher utility for the best responder health state (120-360 µmol/L, 0.765) and lower utility for uncontrolled blood-Phe (>1,201 µmol/L, 0.321) compared to previous sapropterin submission in March 2018 (0.71 and 0.37, respectively)	Moderate. Using utility values from March 2018 for the best (120-360 µmol/L, 0.71) and worst blood-Phe (>1,201 µmol/L, 0.37) categories increased the ICER to \$██████████ ³ , a 37.3% increase.

Source: Constructed during the evaluation.

The redacted values correspond to the following ranges:

¹ \$655,000 to < \$755,000

² > \$1,055,000

³ \$855,000 to < \$955,000

6.73 The proportion of patients who achieve a blood-Phe ≤ 360 µmol/L with pegvaliase treatment was not a key driver of the model. Assuming a relative decrease in response rate of 30% (decreased from 81.8% to 57.3%) only increased the ICER by 3.2%. Given

Public Summary Document – July 2022 PBAC Meeting

than the proportion of patients who achieve a blood-Phe ≤ 360 $\mu\text{mol/L}$ was a key efficacy outcome, this likely reflects the inappropriateness of the assumptions underpinning the economic model.

6.74 The results of the economic model are presented in Table 16.

Table 16: Results of the stepped economic evaluation

Data	Costs			Health outcomes			ICER
	Pegvaliase	Phe-restricted diet	Incremental	Pegvaliase	Phe-restricted diet	Incremental	
Step 1: Response rate with time horizon of 2 years	\$█	\$█	\$█	90.3%	0.00	90.3%	\$█ ¹ per responder
Step 2: Step 1 including extrapolation, background mortality, treatment discontinuation and transformation to QALYs	\$█	\$█	\$█	12.19	8.77	3.42	\$█ ² per QALY
Step 3: Step 2 including continuing treatment criteria	\$█	\$█	\$█	11.98	8.77	3.21	\$█ ² per QALY
Step 4: Step 3 including all resource use	\$█	\$█	\$█	11.98	8.77	3.21	\$█ ² per QALY

Source: Table 3.8-2 (p305) of the submission

ICER = incremental cost-effectiveness ratio; Phe = phenylalanine; QALY = quality-adjusted life year

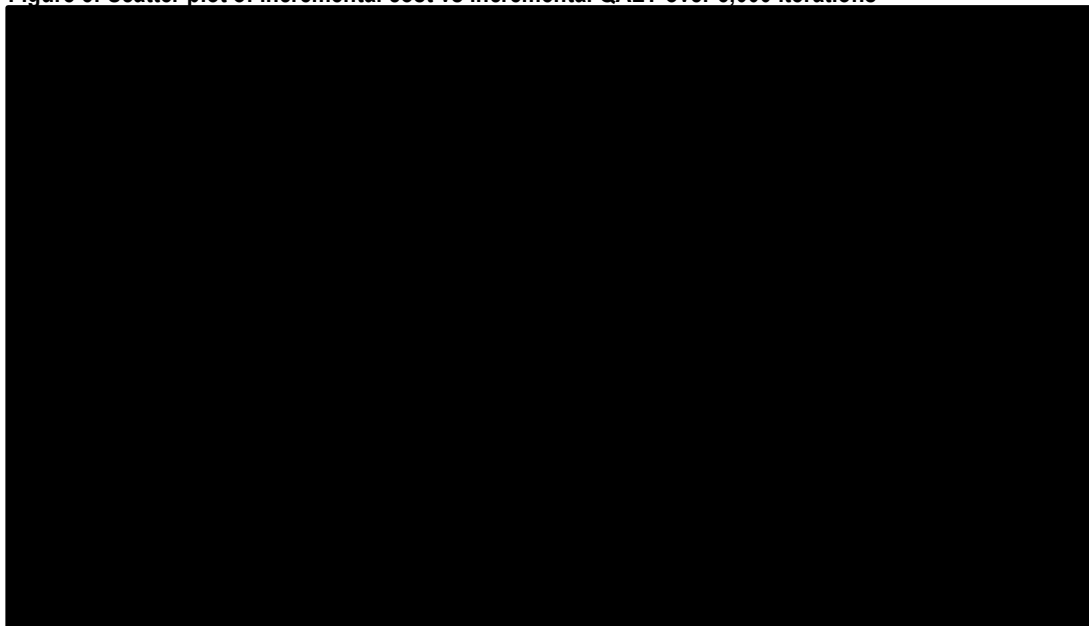
The redacted values correspond to the following ranges:

¹ \$355,000 to < \$455,000

² \$655,000 to < \$755,000

6.75 The submission calculated the ICER using the mean of the costs and the mean of the QALYs from the microsimulation. However, the evaluation noted that there was substantial variation in the ICER (increasing up to > \$1,055,000/QALY) when considering the mean of all the ICERs generated in 5,000 iterations of the model. The ESC considered that this indicated the substantial variability and uncertainty in the model outcomes, due to factors such as the limitations of the underlying clinical data (e.g. there was a large amount of variance in the clinical data and thus poor fit of the data to the regression equations applied for estimating blood Phe levels in the pegvaliase arm). This variability is also indicated in Figure 5, which shows the ICER scatterplot of the model over 5,000 iterations, with each datapoint representing the incremental cost and incremental QALY reported for one iteration (i.e., one patient).

Figure 5: Scatter plot of incremental cost vs incremental QALY over 5,000 iterations



Source: Constructed during the evaluation

- 6.76 The ICER scatterplot shows that in the majority of patients, the incremental cost was above the > \$1,055,000 proposed in the base case, and that a substantial number of iterations had an ICER above the base case ICER as reflected by the number of data points to the left of the willingness to pay line set to the base case ICER of \$655,000 to < \$755,000/QALY. The cluster of data points near the origin (0,0) represents non-responders in the model. In addition, a number of the QALY results were negative – that is, treatment with pegvaliase was correlated with worse outcomes.
- 6.77 Table 17 presents the results of univariate sensitivity analyses.

Public Summary Document – July 2022 PBAC Meeting

Table 17: Univariate sensitivity analyses around economic evaluation

	Incremental Cost	Incremental QALY	ICER (\$/QALY)	Change from baseline
Sensitivity analyses conducted by submission (5,000 iterations)				
Base case (5000 iterations)	\$█	3.21	\$█ ¹	NA
Treat to max. pegvaliase dose (60 mg/day) (base case 30.5 mg/day)	\$█	3.21	\$█ ²	+84.0%
Time horizon = 40 years (base case 100)	\$█	2.96	\$█ ¹	+0.3%
Discount rate: 0% (base case 5%)	\$█	9.48	\$█ ¹	-4.1%
Discount rate: 3.5% (base case 5%)	\$█	4.15	\$█ ¹	-1.4%
Sensitivity analyses conducted during evaluation (100 iterations)				
Base case (100 iterations)	\$█	3.17	\$█ ¹	NA
Time to pegvaliase response 18 months (base case 24 months)	\$█	3.16	\$█ ¹	-0.3%
Time horizon = 2 years (base case 100)	\$█	0.25	\$█ ³	+50.3%
Time horizon = 10 years (base case 100)	\$█	1.29	\$█ ¹	+6.8%
Treat to max. pegvaliase dose (40 mg/day)	\$█	3.17	\$█ ⁴	+23.8%
Pegvaliase responder minimum blood Phe 360 µmol/L (base case 261 µmol/L)	\$█	2.73	\$█ ⁴	+16.4%
Use utilities from March 2018 submission - 0.71 for responder and 0.37 for uncontrolled (0.765 and 0.321 in base case, respectively)	\$█	2.31	\$█ ⁵	+37.3%
Reduce AEMP of one syringe by 10% to \$█ (base case \$█)	\$█	3.17	\$█ ⁶	-9.9%
Reduce AEMP of one syringe by 50% to \$█ (base case \$█)	\$█	3.17	\$█ ⁷	-49.7%
Blood-Phe response rate 57.3% for pegvaliase (base case 81.8%)	\$█	2.40	\$█ ¹	+3.2%

Source: Compiled during the evaluation

The redacted values correspond to the following ranges:

¹ \$655,000 to < \$755,000

² > \$1,055,000

³ \$955,000 to < \$1,055,000

⁴ \$755,000 to < \$855,000

⁵ \$855,000 to < \$955,000

⁶ \$555,000 to < \$655,000

⁷ \$255,000 to < \$355,000

- 6.78 Probabilistic sensitivity analyses around baseline blood-Phe demonstrated that it was a key driver of the model. For example, using the 25th percentiles of baseline Phe, with a value of 953.93 µmol/L, increased the ICER by 84%. The univariate sensitivity analyses showed that other key drivers of the model were the dosage, time horizon, the assumption that pegvaliase responders would achieve a blood-Phe of 261 µmol/L and the utilities used.
- 6.79 The ESC considered that the univariate sensitivity analyses (which adjust assumptions using the existing model structure) did not adequately demonstrate the substantial uncertainty with the model, given the issues with the underlying data and the model structure.
- 6.80 During the evaluation, as an exploratory analysis, an ICER comparing pegvaliase with sapropterin was calculated using the base case QALY and costs for each treatment as

estimated by the submission. An ICER of \$655,000 to < \$755,000/QALY was estimated. However, this result should be interpreted with caution given the issues associated with the model identified above.

Drug cost/patient/year: \$ [REDACTED]

Table 18: Drug cost (maintenance dose) per patient for pegvaliase

	Trial dose and duration	Model	Financial estimates
Mean maintenance dose	NR	30.5 mg/day ^	
Mean duration	Trial ongoing	NR	NR
Cost/patient/week	NC		\$ [REDACTED]

Source: Section 3.6 of the submission; Section 3 workbook, sheet 3a of the utilisation-and-cost-model.

^based on weighted dose of number of treatment days at each dosage, including titration period over five years

NC = not calculable; NR = not reported

- 6.81 The cost of pegvaliase per patient per year calculated in the submission was \$ [REDACTED]. This calculation was based on a maintenance dose of 30.5 mg/day, and 52 weeks of treatment at a cost of \$ [REDACTED] per week.
- 6.82 For reference, the cost of sapropterin for an adult was \$ [REDACTED] per year inclusive of the proposed risk sharing arrangement (RSA), wherein expenditure caps were based on a maximum patient weight of [REDACTED] kg, at a dose of 20 mg/kg (based on the price requested in the sapropterin submission). Using average weight in Australian adults and assuming 40% male, the cost would be \$ [REDACTED] per year without the RSA.

Estimated PBS usage & financial implications

- 6.83 This submission was considered by DUSC. The submission used an epidemiological approach. The financial estimates were based on the sponsor’s requested scenario which also included extending the existing sapropterin listing to allow initiation in adults (Item 6.09, July 2022 PBAC Meeting). Further, the estimates were based on pegvaliase being restricted to use in sapropterin non-responders only.
- 6.84 Key financial inputs for the financial estimates are presented in Table 19.

Public Summary Document – July 2022 PBAC Meeting

Table 19: Key inputs for financial estimates

Parameter	Value applied	Source/ Comment
Prevalence of HPA	1 per 11,226	Boneh et al. (2006). This was consistent with the November 2018 submission.
PKU % of HPA	98.8%	Abadie et al. (2001). This was consistent with the November 2018 submission.
Patients (%) under routine follow-up for PKU	70.0%	Assumption.
Patients (%) with blood Phe levels > 600 µmol/L	49.92%	Literature search. Across 21 studies included in the submission's literature search, the average proportion of patients with blood Phe levels was 49.92% (range: 28% - 100%; median: 75%). Dusc considered that this value is highly uncertain due to the large range in reported values across the studies.
Patients (%) achieving response to sapropterin	23.48%	Additional analyses of PKUDOS based on response rate at 28 days. The evaluation noted this value would be lower if the response rate at 7 days were used, as per PBS restriction. DUSC considered this value is highly uncertain as it is dependent on the uptake rates for sapropterin
Uptake rates	% increasing by % each year to % in 2027 for sapropterin and pegvaliase	Assumption. DUSC considered this value may be underestimated due to the potential for use outside of the restriction.

Source: Table 4.1-1, pp310-313 of the submission; Table 2 of the DUSC Advice.

AEMP = Approved Ex-Manufacturer Price HPA = hyperphenylalaninemia; PKU = phenylketonuria

6.85 Table 20 presents the estimation of the eligible and treated populations.

Table 20: Estimated prevalent eligible and treated population

	2022	2023	2024	2025	2026	2027
Aged ≥ 16 years	21,383,326	21,734,626	22,082,338	22,422,054	22,759,127	23,086,141
HPA (0.0089%)	1	1	1	1	1	1
PKU (98.8%)	1	1	1	1	1	1
Clinic f/u (70%)	1	1	1	1	1	1
>600 µmol/L (49.9%)	1	1	1	1	1	1
Saprop. NR (76.52%)	2	2	1	1	1	1
Eligible population	2	2	1	1	1	1
Uptake rates	%	%	%	%	%	%
Initiating treatment	2	2	2	2	2	2
Continuing in sub. years	0	2	2	2	2	2
Total treated	2	2	2	2	2	2

Source: Table 4.2-1, pp328 of the submission

HPA = hyperphenylalaninemia; PKU = phenylketonuria; f/u = follow-up; Saprop = sapropterin NR = non responder

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² < 500

6.86 The eligible population was calculated in a manner broadly consistent with previous submissions for sapropterin. Specifically, the current submission applied the same inputs for prevalence and percentage of HPA patients who have PKU.

6.87 The submission assumed that 70% of the adult PKU population are under routine follow-up at metabolic clinics. Although DUSC considered that this step was not sufficiently justified and should be removed, the PBAC noted that consultation with clinicians and the MDAA indicated that 70% may be an overestimate and clinicians

Public Summary Document – July 2022 PBAC Meeting

estimated that it is likely that only 50% to 60% of adult patients are under routine follow-up (for example there may be limited access to metabolic clinics in some areas, some patients may have left routine care due to being unable to follow the low protein diet and/or the psychosocial impacts of PKU, or previous historical advice that routine care was not required in adulthood). This assumption may therefore overestimate the number of patients eligible for treatment. However, a new treatment may increase prescriber contact, given that the target population (sapropterin non-responders) have previously demonstrated a willingness to initiate drug therapy for their condition.

6.88 DUSC considered that the treatment uptake rates could be underestimated, but also noted that as pegvaliase is a daily injection, patients may be hesitant to initiate treatment. Additionally, DUSC commented that it is unclear why uptake rates continue to increase over time as patients may not up titrate, due to the requested induction phase and as pegvaliase is associated with high rates of hypersensitivity. DUSC considered the uptake rates observed during the first six months of PBS listing would likely be indicative of future uptake levels.

6.89 Table 21 presents the estimated use and financial implications for pegvaliase.

Table 21: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	1	1	1	1	1	1
Number of scripts dispensed	2	2	2	2	2	2
Estimated financial implications of pegvaliase						
Cost to PBS/RPBS less copayments	\$3	\$3	\$3	\$5	\$5	\$5
Estimated financial implications for Phe-free supplements and premedication						
Cost to PBS/RPBS less copayments	-\$4	-\$4	-\$4	-\$4	-\$4	-\$4
Net financial implications – Pegvaliase						
Net cost to PBS	\$3	\$3	\$5	\$5	\$5	\$5
Net cost to MBS	\$4	\$4	\$4	\$4	\$4	\$4
Net cost to Government	\$3	\$3	\$5	\$5	\$5	\$5
Net financial implications – Sapropterin						
Net cost to Government without RSA	\$4	\$4	\$6	\$6	\$6	\$6
Net cost to Government with RSA	\$4	\$4	\$4	\$4	\$4	\$6
Net financial implications – Pegvaliase plus sapropterin						
Net cost to Government without sapropterin RSA	\$5	\$5	\$7	\$7	\$8	\$8
Net cost to Government with sapropterin RSA	\$3	\$5	\$7	\$7	\$7	\$7

Source: Section 4 of the submission

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ \$30 million to <\$40 million

⁴ \$0 to <\$10 million

Public Summary Document – July 2022 PBAC Meeting

⁵ \$40 million to <\$50 million

⁶ \$10 million to <\$20 million

⁷ \$50 million to <\$60 million

⁸ \$60 million to <\$70 million

- 6.90 The submission estimated that the total cost to the PBS of listing pegvaliase would be \$30 million to < \$40 million in Year 1, increasing to \$40 million to < \$50 million in Year 6, and a total of \$200 million to < \$300 million in the first 6 years of listing.
- 6.91 There is potential for use of pegvaliase outside the requested restriction in all patients (regardless of sapropterin responsiveness), given the positioning of pegvaliase as a third-line therapy may not be clinically justified and given that patients, healthcare providers and patient organisations were not supportive of this approach. This would lead to an overall increase in the expenditure as the estimated cost per year of maintenance with pegvaliase (\$) was substantially higher than the estimated cost per year of maintenance with sapropterin (\$) at the price requested by the sponsor).

Financial Management – Risk Sharing Arrangements

- 6.92 The submission did not propose a risk sharing arrangement (RSA) for pegvaliase.
- 6.93 The existing RSA for sapropterin is based on financial estimates that assume the sponsor would rebate % of the cost to the PBS of all sapropterin used for initial responsiveness testing (and applying a maximum patient body weight of kg). No corresponding rebate for responsiveness testing was proposed for pegvaliase, noting the responsiveness testing period is significantly longer for pegvaliase than it is for sapropterin (up to two years versus seven days, respectively).

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC did not recommend pegvaliase for the treatment of HPA due to PKU in patients aged 16 years and over who are not responsive to sapropterin. The PBAC considered there was a high clinical need in a small patient population, but that the sponsor's proposal to restrict use to patients who are not responsive to sapropterin was inequitable and not clinically appropriate. The PBAC also considered the magnitude of the benefit of pegvaliase was unclear, and that the cost-effectiveness was uncertain and the ICER was exceptionally high at the price proposed.
- 7.2 The PBAC acknowledged the meaningful consumer support and engagement with regards to the submissions for sapropterin and pegvaliase (Item 6.09, which was also considered at the July 2022 PBAC meeting), including a meeting with patient and health professional representatives held prior to the PBAC meeting. In addition, consultation with patients, health professionals and representative organisations assisted in consideration of the appropriate clinical place for sapropterin and pegvaliase.

- 7.3 The consumer input outlined the burden of current management, noting that compliance to the very onerous Phe-restricted diet is unsustainable for many patients, especially in adulthood, and frequently does not reduce blood Phe to an acceptable level. Patients reported that increased protein intake was an important outcome, enabling intake of a broader range of foods and alleviating the substantial quality of life burden associated with a severely low protein diet. In addition, patients and healthcare professionals described the neuropsychiatric symptoms associated with high Phe levels including psychosocial aspects, impacts on cognitive function and the ability to manage self-care and tasks on a daily basis. Clinicians stated that the benefits of reducing blood Phe levels in adults are significant and meaningful, with depression and anxiety scores improved and working memory and cognitive function substantially improved or returned over the longer term. Clinicians also highlighted that there is evidence that patients experience reversible changes in white matter indicative of neurodegenerative effects of raised blood Phe levels.
- 7.4 The PBAC noted that many consumers, healthcare professionals and patient organisations considered that the sponsor's proposed clinical place for pegvaliase, which was in sapropterin non-responders (i.e., patients who do not meet the criteria for response to sapropterin), was not appropriate. Consumers outlined that it was potentially inequitable as it would exclude some patients who may benefit from pegvaliase (e.g., patients who are responding sub-optimally to sapropterin). Further, the PBAC considered that it was inconsistent with the clinical evidence and was not clinically appropriate noting that limited exploratory subgroup analyses suggested that sapropterin responder-status was not a treatment effect modifier (see paragraph 6.41). Overall, the PBAC considered that sponsor's proposal to restrict pegvaliase to sapropterin non-responders was not appropriate.
- 7.5 The proposed restriction defined a response to pegvaliase as either: (a) blood-Phe < 360 µmol/L; or (b) the achievement of a clinically meaningful reduction from pegvaliase-naïve baseline in the ADHD-RS. The PBAC considered that it may not be appropriate to assess initial response based on a single blood-Phe < 360 µmol/L measurement as Phe levels can fluctuate from day-to-day and in response to variation in dietary Phe intake. Additionally, the PBAC noted that the submission did not provide any comparative clinical data to support a claim of superiority in ADHD-RS inattention subscale score. The PBAC noted that consumers and clinicians had outlined that other factors may also be important markers of a meaningful improvement for patients, such as protein tolerance/dietary Phe intake, quality of life and an assessment as to how well a patient is managing with their current regimen. Overall, the PBAC considered that the most appropriate response criteria for pegvaliase remained unclear.
- 7.6 The PBAC considered that the nominated comparator, a Phe-restricted diet alone, was an appropriate comparator in the context of the restriction proposed by the submission. However, the PBAC considered that sapropterin was also a relevant comparator, given it had considered that the proposed restriction of pegvaliase to

sapropterin non-responders was not appropriate. Further, the PBAC noted that for many patients, a major goal of treatment is relaxation of the strict diet. Consequently, pegvaliase may in practice, partly replace the Phe-restricted diet.

- 7.7 The PBAC noted that the submission presented an eight week randomised trial (PRISM 2 Part 2) comparing pegvaliase to placebo. The other clinical evidence presented consisted of single-arm open label pegvaliase studies, a matched-cohort analysis without a common comparator arm, and a naïve indirect comparison. The PBAC considered there was a very high level of uncertainty in the clinical evidence and comparative effectiveness estimates, and that the submission had likely overestimated the benefit and underestimated the comparative harms of pegvaliase because: 1) there was a high rate of attrition in the PRISM trials; and 2) PRISM 2 Part 2 only included patients who had received pegvaliase for a significant period of time and had achieved $\geq 20\%$ reduction in blood-Phe. As such the clinical data reflected patients who already had a degree of responsiveness and tolerability to pegvaliase.
- 7.8 The PBAC considered that while pegvaliase appears to be effective at reducing blood Phe-levels, the magnitude of the incremental benefit could not be reliably estimated and was likely overestimated by the submission due to the poor quality and methodological limitations of the clinical evidence.
- 7.9 The PBAC considered that the supportive evidence from the literature suggests that a reduction in blood-Phe is plausibly related to a reduction in neuropsychiatric symptoms though this difference was difficult to quantify. Overall, the PBAC considered that the benefit from pegvaliase in terms of patient-relevant outcomes such executive functioning was not well-demonstrated in the clinical data. The PBAC considered that, while consumer input assisted in establishing the benefit of lowering blood-Phe levels in adult patients, the degree of benefit with pegvaliase remained uncertain given the available clinical data.
- 7.10 The PBAC considered the claim of inferior safety compared with a Phe-restricted diet alone was supported, however given the lack of longer-term comparative data the magnitude of the difference over a longer treatment period was uncertain. Further, the PBAC noted that patients who discontinued pegvaliase due to intolerance to therapy in PRISM 1 or PRISM 2 Part 1 were not included in PRISM 2 Part 2 and therefore the AE rates presented in the submission, particularly those relating to its immunogenicity (e.g., anaphylaxis, hypersensitivity, generalised skin reaction) are likely to underestimate the true burden of AEs for pegvaliase.
- 7.11 The PBAC noted that the ESC considered the economic model was highly uncertain and not informative for decision-making purposes. The ESC considered that the complex approach, extrapolated over a 100 year time horizon, meant the limitations of the clinical data (e.g., the low sample sizes and wide variances) were magnified. The PBAC also noted the ESC's advice that there were a number of other areas of the model that increased uncertainty and appeared to overestimate the ICER:

Public Summary Document – July 2022 PBAC Meeting

- The regression equations used to estimate blood-Phe levels over time in the pegvaliase arm had poor model fit and were not well-justified.
 - The model assumed patients treated with a Phe-restricted diet were unable to achieve a response, which was inconsistent with the clinical evidence provided.
 - Utilities were less conservative than those applied in the March 2018 sapropterin submission, which favoured pegvaliase. Further, it was unclear if the health states from the TTO study adequately aligned with the specific Phe values used in the model.
 - The pegvaliase dose was underestimated compared with clinical practice (due to the use of study data that included a titration period, which was extrapolated over a lifetime).
- 7.12 The PBAC noted that the ICER of \$655,000 to < \$755,000/QALY was substantially higher than the ICER that had previously been calculated for sapropterin in adults with non-maternal PKU (\$355,000 to < \$455,000/QALY), which the PBAC previously considered was not cost-effective (para 7.3, sapropterin PSD, November 2020 PBAC meeting). The PBAC also noted the proposed cost per patient per year for pegvaliase was substantially higher than proposed (although not accepted by the PBAC) for sapropterin (\$| versus \$|). The PBAC considered the cost-effectiveness was uncertain and the ICER was exceptionally high at the price proposed. The PBAC considered that the ICER for pegvaliase should be no higher than that accepted for sapropterin for initiation in adult patients.
- 7.13 The PBAC noted that the financial estimates were based on pegvaliase use being restricted to sapropterin non-responders only, which the PBAC considered was inappropriate (paragraph 7.4). The PBAC noted that a broader restriction (allowing use in patients regardless of sapropterin responsiveness) would increase the utilisation estimates. The PBAC considered that the proportion of adult PKU population who are under routine follow-up at metabolic clinics was likely overestimated, noting that for sapropterin it had considered that this proportion should be reduced from 70% to 55%. The PBAC also considered that the uptake rates were uncertain and may have been overestimated given that access to pegvaliase may be constrained by the availability of metabolic clinics (as outlined in paragraph 6.15).
- 7.14 The PBAC considered that any resubmission for pegvaliase should not restrict access based on prior response to sapropterin and hence sapropterin should be included as a comparator.
- 7.15 The PBAC noted that a resubmission for pegvaliase may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.
- 7.16 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not recommended

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

BioMarin thanks the PBAC for acknowledging the high clinical need in this small patient population, and looks forward to working with the PBAC to identify the appropriate place for pegvaliase in the treatment of PKU, so that it can be made available on the PBS.