7.03 PEGVALIASE,
Injection 2.5 mg in 0.5 mL pre-filled syringe
Injection 10 mg in 0.5 mL pre-filled syringe
Injection 20 mg in 1 mL pre-filled syringe,
Palynziq®,
BioMarin Pharmaceutical Australia Pty Ltd.

1 Purpose of submission

1.1 The standard re-entry submission requested listing of pegvaliase for the treatment of patients aged 16 years and older with phenylketonuria (PKU) who have inadequate blood phenylalanine (Phe) control (baseline blood Phe level above 600 micromoles per litre [µmol/L]) despite prior management with available treatment options including a Phe restricted diet and sapropterin. The resubmission also sought listing for patients aged 16 years and older with PKU who have a protein tolerance of less than 15 grams per day, even if the patient has met the PBS criteria for sapropterin responsiveness (i.e. ≥ 30% reduction in blood Phe from baseline).

1.2 While the PBAC did not previously recommend pegvaliase for the treatment of hyperphenylalaninaemia (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 (paragraph 7.1, pegvaliase, Public Summary Document, July 2022 PBAC meeting).

1.3 Listing for pegvaliase was requested on the basis of a cost-utility analysis versus a Phe-restricted diet.

1.4 The key components of the clinical issue addressed by the resubmission 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 aged 16 years are or older, have blood phenylalanine levels ≥ 600 micromole/litre (µmol/L) and who are not responsive to sapropterin or who have a daily protein tolerance of less than 15 grams per day.[a]
Intervention	Pegvaliase administered as a subcutaneous injection at a maintenance dose of 20-60 mg daily after induction and titration per the pegvaliase product information document
Comparator	Phe-restricted diet alone
Outcomes	Reduction in blood Phe levels to < 360 µmol/L or a clinically meaningful reduction in the inattention subscale of the ADHD-RS score (defined as a reduction of at least 5) from pegvaliase-naïve baseline.
Clinical claim	Pegvaliase is superior to a Phe-restricted diet for the composite outcome of response (Phe levels or ADHD-RS score). Pegvaliase has inferior safety outcomes compared with a Phe-restricted diet.

Source: Table 1.1-1, p14 of the resubmission.
ADHD-RS = Attention Deficit Hyperactivity Disorder Rating Scale; HPA = hyperphenylalaninemia; Phe = phenylalanine; PKU = phenylketonuria
[a] Underlined text indicates change compared to the previous submission.

2 Background

Registration status

2.1 Pegvaliase was granted orphan drug designation by the TGA on 1 April 2020 and was TGA registered on 14th July 2021. The TGA-registered indication for pegvaliase is "for the treatment of patients with phenylketonuria (PKU) aged 16 years and older who have inadequate blood phenylalanine control despite prior management with available treatment options".

2.2 No explicit definition was provided regarding 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 resubmission for pegvaliase considered by the PBAC.

2.4 The key issues in the July 2022 pegvaliase submission and how the resubmission addresses these issues are presented in Table 2.

Table 2: Summary of key matters of concern

Component	Matter of concern	Evaluation comments on how the resubmission addressed it
Proposed restriction	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 (paragraph 7.1, pegvaliase Public Summary Document [PSD], July 2022 PBAC meeting).	Partially addressed. While the resubmission's proposed restriction included pegvaliase use in an additional patient population who have a daily protein tolerance of less than 15 grams per day (in patients who have responded to sapropterin), the evaluation considered such use may not be consistent with the pegvaliase TGA-approved indication that requires patients to have had inadequate blood Phe control despite prior management with available treatment options. Refer to paragraphs 3.4 to 3.7 for details.
Proposed restriction response criteria	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 (≥ 5 points). The PBAC considered that the most appropriate response criteria for pegvaliase remained unclear. 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 (paragraph 7.5, pegvaliase PSD, July 2022 PBAC meeting).	Not adequately addressed. The proposed pegvaliase response criteria remained the same as in the previous submission. Consequently, demonstration of a response to treatment remained based on a single blood-Phe measurement. Refer to paragraphs 3.8 to 3.10 for details. The proposed demonstration of response to pegvaliase is different to the demonstration of response in the sapropterin PBS restriction, that requires patients have ≥ 30% reduction in Phe levels from baseline during initial responsiveness testing. As in the previous submission, the resubmission did not provide any comparative clinical data to support the superiority claim in ADHD-RS inattention subscale score.
Proposed restriction, maximum duration of initiation treatment	The proposed restriction allowed up to 24 months treatment under the initial treatment phase (induction, titration and maintenance) before a treatment response must be demonstrated. 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 (paragraph 3.3, pegvaliase PSD, July 2022 PBAC meeting).	Not addressed. The proposed restriction in the resubmission allowed up to 24 months treatment under the initial treatment phase. The resubmission provided new dispensing data and claimed these data demonstrate that it may take up to 24 months to reach a therapeutic dose of pegvaliase. The resubmission also claimed there are other examples of a long initial treatment period on the PBS such as tyrosine kinase inhibitors for the treatment of chronic myeloid leukaemia. Refer to paragraphs 3.11 to 3.12 for details.

Component	Matter of concern	Evaluation comments on how the resubmission addressed it
Comparator	While 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, the Committee 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 (paragraph 7.6, pegvaliase PSD, July 2022 PBAC meeting). 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 (paragraph 7.14, pegvaliase PSD, July 2022 PBAC meeting).	Not addressed. The same comparator of Phe-restricted diet alone was proposed in the resubmission. Although it may provide a relevant comparator for the additional patient population who had previously responded to sapropterin, sapropterin was not nominated as a comparator. Refer to paragraphs 5.1 to 5.5 for details.
Clinical effectiveness	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 (paragraph 7.8, pegvaliase PSD, July 2022 PBAC meeting).	Not adequately addressed. The resubmission did not provide any additional data that allowed the demonstration of the magnitude of the incremental benefit for pegvaliase. The only new clinical evidence provided in the resubmission was an additional analysis (Burton 2024). Burton 2024 compared pegvaliase-treated and Phe-restricted 'diet alone'-treated patients using the same data as presented in the previous submission (PRISM vs PKUDOS). Refer to paragraphs 6.13 to 6.30 for details.
Economic evaluation	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 (paragraph 7.11, pegvaliase PSD, July 2022 PBAC meeting). Additionally, the PBAC noted that some inputs in the 2022 model favoured pegvaliase (utilities, pegvaliase dose and comparative harms), which would potentially lead to the ICER being underestimated (paragraphs 6.70, 6.72 and 7.10, pegvaliase PSD, July 2022 PBAC meeting).	Not adequately addressed. The same economic model and microsimulation approach were used in the resubmission. Refer to paragraphs 6.44 to 6.64 for details.

Component	Matter of concern	Evaluation comments on how the resubmission addressed it
ICER	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 (paragraph 7.12, pegvaliase PSD, July 2022 PBAC meeting).	Partially addressed. The resubmission reduced the proposed pegvaliase cost from $[redacted] to $[redacted] per syringe, however there was considerable uncertainty regarding the resubmission's estimated cost which was based on [redacted] Consequently, there is a high degree of uncertainty for the pegvaliase cost which is dependent on the implementation of the proposed RSA.
Financial estimates, patient population	For the 2022 submission, 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 (paragraph 7.13, pegvaliase PSD, July 2022 PBAC meeting).	Not addressed. While the resubmission included the additional patient population of sapropterin responders who have a daily protein tolerance of less than 15 grams per day, the resubmission's financial estimates did not include this patient population and the resubmission assumed there would not be an increase in utilisation estimates.
Financial estimates, inputs	The PBAC considered that the proportion of adult PKU population who are under routine follow-up at metabolic clinics and pegvaliase uptake rates were likely overestimated (paragraph 7.13, pegvaliase PSD, July 2022 PBAC meeting).	Not addressed. The resubmission used the same inputs as in the previous submission. These inputs were used to establish the RSA proposed in the resubmission.

Source: Pegvaliase July 2022 PSD

ADHD-RS = Attention Deficit Hyperactivity Disorder Rating Scale; AEMP = approved ex-manufacturer price; ICER = incremental cost-effectiveness ratio; Phe = phenylalanine; PKU = phenylketonuria; PSD = public summary document; RSA = Risk Sharing Arrangement

3 Requested listing

3.1 The listing requested by the sponsor is outlined below.

Name, Manner of administration and form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed Price for Max. Qty [d]	Available brands
Initiation treatment					
PEGVALIASE, 1 x 2.5 mg pre-filled syringe, sc. Injection	1 [a]	1 [b]	-[a]	$584.56 published price	Palynziq
PEGVALIASE, 1 x 10 mg pre-filled syringe, sc. injection	1 [a]	1 [b]	-[a]	$584.56 published price	Palynziq
PEGVALIASE, 10 x 20 mg pre-filled syringe, sc. injection	1 [a]	10 [b]	-[a]	$5,262.93 published price	Palynziq
Continuing treatment					
PEGVALIASE, 1 x 2.5 mg pre-filled syringe, sc. injection	1 [c]	1 [b]	5	$584.56 published price	Palynziq
PEGVALIASE, 1 x 10 mg pre-filled syringe, sc. injection	1 [c]	1 [b]	5	$584.56 published price	Palynziq
PEGVALIASE, 10 x 20 mg pre-filled syringe, sc. injection	1 [c]	10 [c]	5	$5,262.93 published price	Palynziq
Category/Program:	General Schedule				
Restriction type:	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) within first 24 months**
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 sapropterin in accordance with the PBS restriction for sapropterin ('Initial treatment - responsiveness testing' and 'First continuing treatment') OR Patient must have a daily protein tolerance of less than 15 grams per day AND Treatment must not be in combination with sapropterin
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 AND 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)
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 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 and the appropriate number of repeats, 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 5 months 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:	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:	**Maintenance treatment**
Clinical criteria:	Patient must have previously received PBS-subsidised treatment under the Initial treatment (induction, titration, and maintenance) restriction with this drug for this condition AND Patient must have demonstrated a response to initial treatment with this drug, assessed at a minimum of a minimum of 21 weeks and up to 24 months from commencing treatment with this drug, 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 Patient must be undergoing regular phenylalanine testing and assessment of adherence to dietary modifications.
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, prescribers should request the appropriate quantity of prefilled syringes, required to provide 6 months of treatment at a dose of 60 mg per day or the patient's maximum tolerated dose. 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.
Administrative advice:	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. No increase in the maximum quantity or number of units may be authorised. **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: 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.

Source: Tables 1.4-5 and 1.4-5, p46-48 of the resubmission.
Underlined text indicates change compared to the previous submission.
AEMP = approved ex-manufacturer price; RSA = Risk Sharing Arrangement; sc. = subcutaneous
[a] The medical practitioner should request the appropriate number of syringes and repeats for the strength of pegvaliase required by the patient depending on the phase of dosing regimen.
[b] Depends on the maximum quantity of packs requested.
[c] Maximum dose of pegvaliase 60 mg/day.
[d] The DPMQ shown is for a maximum quantity of one pack.

3.2 The resubmission proposed a published ex-manufacturer price (EMP) of $510 per syringe, regardless of the dose. Rather than a Special Pricing Arrangement with an effective price, the resubmission proposed a Risk Sharing Arrangement (RSA) with a [redacted] Commonwealth expenditure caps, which the resubmission estimated [redacted] However as discussed in paragraphs 6.83 to 6.87, [redacted]

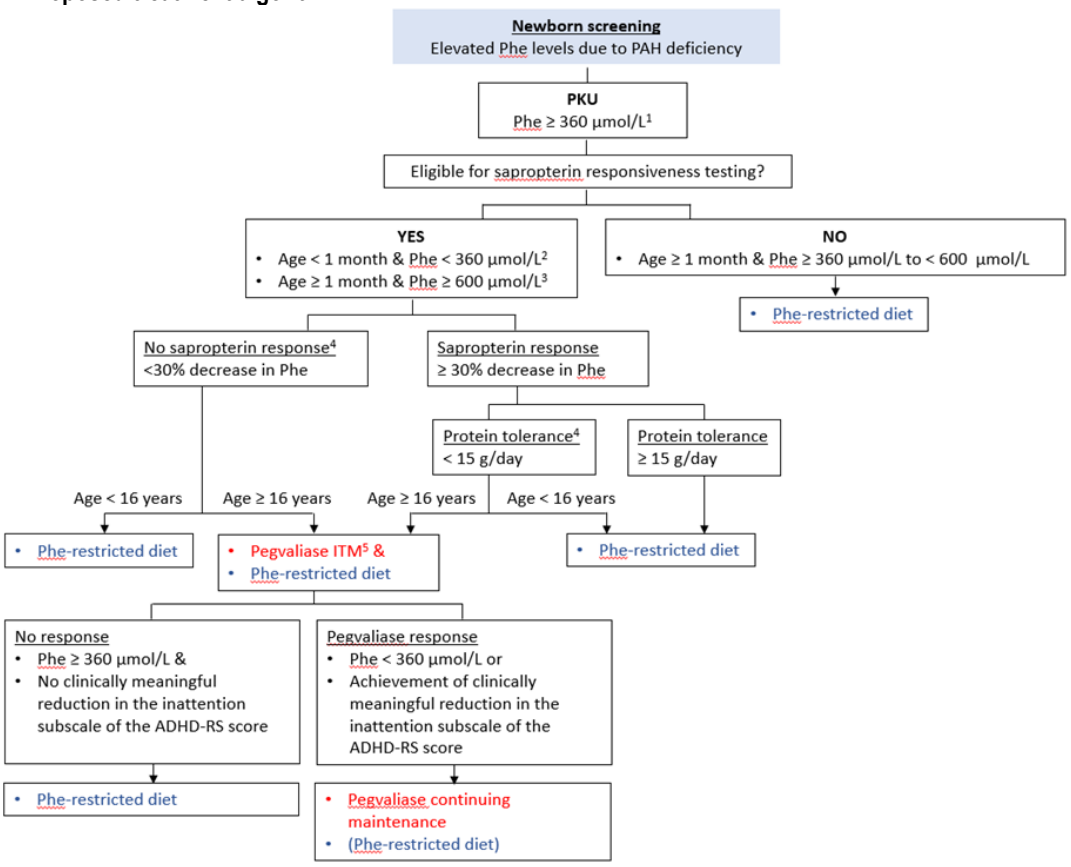
3.3 The previous submission proposed an effective EMP of $[redacted] per syringe (through a Special Pricing Arrangement, rather than an RSA [redacted]).

Patient population

3.4 As in the previous submission, the resubmission requested PBS listing of pegvaliase for patients who have failed to achieve an 'adequate response' to a trial of sapropterin. In the sapropterin PBS criteria, an adequate response is defined as a ≥ 30% reduction in blood Phe from baseline (following initial treatment with

sapropterin). The resubmission also requested PBS listing for an additional patient population who have experienced an adequate response to a trial of sapropterin (per the PBS criteria) but who have a daily protein tolerance of less than 15 grams per day. Refer to Figure 1 for details of where these patient populations sit within the proposed PKU treatment algorithm.

Figure 1: Proposed treatment algorithm



Source: Figure 1.2-2, p39 of the resubmission
Note: Pegvaliase must be used with a Phe restricted diet.
ADHD-RS = Attention Deficit Hyperactivity Disorder Rating Scale; ITM = induction, titration and maintenance; MDDA = Metabolic Dietary Disorders Association; Phe = phenylalanine; PKU = phenylketonuria
[1] Patients with blood Phe > 120 and < 360 µmol/L monitored until school age, if blood Phe ≥ 360 µmol/L commence treatment for PKU
[2] Sapropterin responsiveness test is conducted over 24 h for a patient less than one month of age
[3] Sapropterin responsiveness test is conducted over 7 days for a patient age more than one month
[4] The MDDA has requested the inclusion of patients with a protein tolerance < 15 g/day, which may include a small number of sapropterin-responsive patients. However, clinicians have advised that most of these patients are likely to suffer from classical PKU, which is characterised by very low or no residual protein activity, and unlikely to be sapropterin responsive.
[5] Pegvaliase requires gradual dose escalation using the recommended induction, titration and maintenance (ITM) dosing regimen designed to reduce the risk of hypersensitivity reactions, which occur mainly in the early phases of treatment. Patients may be treated with pegvaliase for up to 24 months under the proposed initial PBS restriction to allow patients to reach a therapeutic dose of pegvaliase.

3.5 In July 2022, the PBAC considered that the sponsor's proposed clinical place 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 (paragraph 7.4, pegvaliase Public Summary Document [PSD], July 2022 PBAC meeting). The resubmission claimed that while it

would be preferable to position pegvaliase alongside sapropterin in the clinical treatment algorithm, this place in therapy could not be supported on the grounds of commercial viability.

3.6 The resubmission stated that external stakeholders, including metabolic physicians, nurses, dieticians and the Metabolic Dietary Disorders Association (MDDA) have expressed their support for the requested listing if it results in access to pegvaliase rather than the current situation where no patient has PBS-subsidised access. The resubmission highlighted while the MDDA have indicated their overall support, it expressed a desire to include the additional patient population who have protein tolerance of less than 15 g per day, even if responsive to sapropterin (i.e. meet the PBS criteria of ≥ 30% reduction in blood Phe from baseline). The resubmission claimed that clinicians have advised that most of these patients are likely to have classical PKU (characterised by very low/no residual protein activity) and are unlikely to achieve a response to sapropterin; however, the resubmission acknowledged that there may be a small number of sapropterin-responsive patients who have a protein tolerance of less than 15 g per day, and these patients would be eligible under the proposed restriction.

3.7 The TGA-approved indication for pegvaliase is "for the treatment of patients with PKU aged 16 years and older who have inadequate blood Phe control despite management with available treatment options", however the evaluation considered that this does not necessarily align with the proposed pegvaliase PBS restriction and the current sapropterin PBS restriction. This is because there may be some patients who meet the pegvaliase initiation criteria (i.e. due to having a protein tolerance of < 15g per day) who do not have 'inadequate blood Phe control' (often defined in trials as levels > 600 µmol/L) while on sapropterin. The PBAC noted that clinicians indicated that these patients would not be considered to have an adequate response to sapropterin in clinical practice.

Response assessment

3.8 As in the July 2022 submission, the restriction proposed in the resubmission allows up to 24 months treatment under the initial treatment phase (induction, titration and maintenance) before a treatment response must be demonstrated. For the previous submission, the PBAC noted "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. The ESC previously 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 previously considered that a shorter period for assessing response would be more appropriate" (paragraph 3.3, pegvaliase PSD, July 2022 PBAC meeting).

3.9 The requested pegvaliase continuing restriction was consistent with the previous submission and required that patients must have demonstrated a response to initial treatment assessed at a minimum of 21 weeks and up to 24 months from commencing treatment, defined as at least one of either Phe blood level < 360 µmol/L or a ≥ 5-point improvement in the inattention subscale of the Attention Deficit Hyperactivity Disorder Rating Scale (ADHD-RS) score. There was no proposed requirement for demonstration of continued response over time. Previously, the ESC considered this may be inappropriate as the ADHD-RS inattention subscale score and the nominated minimally clinically important difference (MCID) have not been validated for use in PKU patients (paragraph 3.6, pegvaliase PSD, July 2022 PBAC meeting). The resubmission did not provide data to demonstrate validation of the nominated MCID in patients with PKU.

3.10 For the previous submission, "(t)he 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" (paragraph 7.5, pegvaliase PSD, July 2022 PBAC meeting). As in the previous submission, the resubmission did not provide any comparative clinical data to support a claim of superiority in ADHD-RS inattention subscale score.

3.11 The resubmission claimed that new dispensing data shows that up to 24 months may be required to reach a therapeutic dose of pegvaliase. The resubmission provided additional dispensing data from the sponsor's database associated with the pegvaliase Risk Evaluation and Mitigation Strategy (REMS) in the United States (Lah 2022) and unpublished data. While Lah 2022 reported that the upper interquartile limit for the time to reach a dose of 60 mg of pegvaliase was 95.3 weeks, the time to maximum dose was considerably lower (mean = 31.8 weeks; interquartile range = 9.7 to 45.0 weeks; median = 18.6 weeks). The evaluation and the ESC therefore considered that it remained unclear if it was reasonable to allow all patients to receive up to 24 months of pegvaliase treatment before being required to demonstrate a response to initial treatment.

3.12 The resubmission acknowledged that 24 months is a long period for titration of a medicine but noted that there are other examples of a long initial treatment period before response is assessed, such as the tyrosine kinase inhibitors (e.g., imatinib,

nilotinib, ponatinib and asciminib) for the treatment of chronic myeloid leukaemia. While there are examples of PBS restrictions for tyrosine kinase inhibitors allowing an 18-month initial treatment period before a response is required, their continued treatment often requires subsequent demonstration of treatment response. For example, the PBS restrictions for imatinib and nilotinib for the treatment of chronic myeloid leukaemia (chronic phase) state that continuing therapy is dependent on patients demonstrating a response to imatinib therapy following the initial 18 months of treatment and at 12 monthly intervals thereafter. No current PBS restrictions allowing a 24-month initial treatment period before a response is required were identified.

Other

3.13 Under the proposed restriction, patients defined as having a response to sapropterin but having protein tolerance of less than 15 g/day would be eligible to receive pegvaliase. However, these patients would be required to cease sapropterin to initiate pegvaliase, even though they had demonstrated a response to sapropterin. The evaluation considered it was unclear if this would be reasonable. However, the PBAC noted that clinicians indicated that these patients would not be considered to have an adequate response to sapropterin in clinical practice (refer to paragraph 6.4), and also considered that the restriction should allow patients to switch back to sapropterin if they experience an inadequate response or intolerance to pegvaliase.

3.14 While the proposed treatment algorithm (see Figure 1) shows a division of patients who respond to sapropterin based on whether they have a protein tolerance of less than or equal to/greater than 15 g/day, the existing sapropterin PBS restriction does not include any requirement of response based on protein tolerance. The potential switching of some sapropterin responders to receive pegvaliase was not considered as part of the previous economic decision making when sapropterin was recommended by the PBAC. Consequently, the evaluation considered that changing the treatment algorithm for these patients may have implications for the cost-effectiveness of patients receiving sapropterin that have not been evaluated.

3.15 The resubmission requested that pegvaliase can be prescribed by either a metabolic physician or a nurse practitioner (initial and maintenance treatment). This request was different to the previous submission, where it was requested that pegvaliase be prescribed by a metabolic physician (initial and maintenance treatment) or by a nurse practitioner (maintenance treatment only). The evaluation considered that it was unclear whether it would be appropriate for nurse practitioners to prescribe initial treatment of pegvaliase. Under the current PBS initial treatment – responsiveness testing listing for sapropterin, patients must be treated by a metabolic physician. For continuing treatment (first and subsequent), patients receiving sapropterin can then be treated by a metabolic physician or a nurse practitioner experienced in the treatment of phenylketonuria in consultation with a metabolic physician. At its March 2025 meeting, in its review of nurse practitioner/endorsed midwife prescribing, the

PBAC considered a request to permit nurse practitioner prescribing of initial sapropterin treatment, noting that nurse practitioners were already eligible to prescribe continuing treatment. In March 2025, the PBAC did not recommend nurse practitioners be eligible to authorise initial PBS-subsidy for sapropterin based on the view that HPA due to PKU is a complex condition where specialists (metabolic physicians) are likely to have the expertise required in making the diagnosis and overseeing initial treatment. Refer to paragraph 7.9.

3.16 The pegvaliase Product Information (PI) states 'patients should be instructed to carry an adrenaline injection device with them at all times during pegvaliase treatment.' PBS supply of adrenaline pens must be initiated by, or in consultation with a clinical immunologist / allergist / paediatrician / respiratory physician (or patients discharged from hospital or an emergency department after treatment with adrenaline). The proposed restrictions included a 'Caution' note about the risk of acute systemic hypersensitivity reactions when using pegvaliase, and the Secretariat has made amendments to specify that patients should be prescribed an adrenaline auto-injector as per the TGA PI. However, the evaluation considered that it was unclear how patients would access an adrenaline auto-injector. The Pre-Sub-Committee-Response (PSCR) stated "all metabolic physicians consult with relevant specialists (i.e., paediatrician, clinical immunologist, allergist, or respiratory physician) and provide their name at the time of the initial Authority Required Application for PBS supply of an adrenaline injection device.". Refer to paragraph 7.8.

3.17 The listing requested by the sponsor, with changes suggested by the Secretariat (additions are in italics and deletions are in strikethrough), based on the PBAC outcome section (paragraphs 7.6 to 7.9) is shown below (noting further amendments may be required as part of the deferral process).

Initial treatment: (Induction, titration, and maintenance treatment) within the first 24 months of therapy

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
PEGVALIASE					
pegvaliase 2.5 mg/0.5 mL injection, 0.5 mL syringe	NEW	~~1~~ *6*	~~1~~ *6*	*0*	Palynziq
pegvaliase 10 mg/0.5 mL injection, 0.5 mL syringe	NEW	~~1~~ *14*	~~1~~ *14*	*0*	
pegvaliase 20 mg/mL injection, 10 x 1 mL syringe	NEW	~~1~~ *9*	~~1~~ *90*	*5*	
Category / Program: ☒ GENERAL - General Schedule (Code GE)					
Prescriber type: ☒ Medical Practitioners ☒ *Nurse Practitioners*					
Benefit type: ☒ Authority Required (Telephone/ Online PBS Authorities System)					
Prescribing rule level:					
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.					
Administrative Advice:					

No increase in the maximum number of repeats may be authorised.
Administrative Advice: 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 with pegvaliase is associated with acute systemic hypersensitivity reactions. At first dose administration, patients should be monitored for at least 60 minutes at a medical facility capable of managing acute systemic hypersensitivity reactions. Patients should be prescribed an adrenaline auto-injector in the case of acute systemic hypersensitivity reactions and educated on how to recognise the signs and symptoms. Refer to the approved Therapeutic Goods Administration (TGA) Product Information for administration and monitoring requirements.*
Restriction Summary [new1] / Treatment of Concept: [new1A]
Indication: Hyperphenylalaninaemia (HPA) due to phenylketonuria (PKU)
Treatment Phase: Initial treatment (Induction, titration, and maintenance treatment) within the first 24 months of therapy
~~***Clinical criteria:***~~
~~Patient must not have previously received PBS-subsidised treatment with this drug for this condition~~
~~**AND**~~
Clinical criteria:
Patient must have a baseline blood phenylalanine level above 600 micromole per L
AND
Clinical criteria:
~~Patient must have failed to achieve an adequate response to a trial of sapropterin in accordance with the PBS restriction for sapropterin ('Initial treatment - responsiveness testing' and 'First continuing treatment') OR~~ *Patient must not have achieved an adequate response to sapropterin treatment defined as demonstrating greater than or equal to a 30% reduction in phenylalanine levels from baseline; OR*
Patient must have a daily protein tolerance of less than 15 grams per day.
AND
Clinical criteria:
The treatment must not be in combination with sapropterin
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~~ *Must be treated by a health practitioner who is any of (i) a medical practitioner, (ii) a nurse practitioner in consultation with a metabolic physician*
~~**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.~~
Prescribing Instructions: Patient must not receive more than 24 months of treatment under this restriction.
Prescribing Instructions:

Confirmation of eligibility for treatment with diagnostic reports must be documented in the patient's medical records.
Prescribing Instructions: ~~At the time of the authority application, medical practitioners should request the appropriate quantity of prefilled syringes and the appropriate number of repeats, based on the dose required and in accordance with the recommended dosing described in the pegvaliase Product Information~~ *At the time of authority application, prescribers must request the appropriate number of prefilled syringes of each strength, to provide sufficient drug for 1 month of treatment at the dosage regimen specified in the approved Therapeutic Goods Administration (TGA) Product Information (PI). A separate authority prescription form must be completed for each strength requested.* ***The maximum listed quantity** or number of repeats **must not be prescribed** if lesser quantity or repeats are sufficient for the patient's needs.*
Prescribing Instructions: ~~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)~~ ~~*An assessment of a patient's response to the initial course of treatment must be conducted following a minimum of 5 months of therapy.*~~ *An adequate response to this drug is defined as a blood phenylalanine level below 360 micromole per L.*
Prescribing Instructions: ~~A response to initial treatment must be assessed following a minimum of 5 months 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.~~ *An assessment of a patient's response to the initial course of treatment must be conducted following a minimum of 5 months of therapy.* *Patients who demonstrate a response are eligible to transition to PBS subsidised treatment under the maintenance treatment restriction.* *Patients who do not demonstrate a response may continue treatment under this restriction up to a maximum total duration of 18 months of therapy. Prescribers must reassess the patient at 18 months to determine the following:* *(i) If no response is demonstrated, treatment should be discontinued.* ***(ii)** If an improvement in protein tolerance and/or neurocognitive function is demonstrated, treatment may be continued for a further 6 months only (total duration of 24 months of therapy).*

Maintenance treatment:

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
PEGVALIASE					
pegvaliase 2.5 mg/0.5 mL injection, 0.5 mL syringe	NEW	~~1~~ *56*	~~1~~ *84*	5	Palynziq
pegvaliase 10 mg/0.5 mL injection, 0.5 mL syringe	NEW	~~1~~ *28*	~~1~~ *28*	5	
pegvaliase 20 mg/mL injection, 10 x 1 mL syringe	NEW	~~1~~ *9*	~~10~~ *90*	5	
Category / Program: ☒ GENERAL - General Schedule (Code GE)					
Prescriber type: ☒ Medical Practitioners ☒ Nurse Practitioners					
Benefit type: ☒ Authority Required (Telephone/ Online PBS Authorities System)					
Prescribing rule level:					

Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: *No increase in the maximum number of repeats may be authorised.*
Administrative Advice: 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.
~~**Administrative Advice:**~~ ~~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.~~
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 with pegvaliase is associated with acute systemic hypersensitivity reactions. At first dose administration, patients should be monitored for at least 60 minutes at a medical facility capable of managing acute systemic hypersensitivity reactions. Patients should be prescribed an adrenaline auto-injector in the case of acute systemic hypersensitivity reactions and educated on how to recognise the signs and symptoms. Refer to the approved Therapeutic Goods Administration (TGA) Product Information for administration and monitoring requirements.*
Restriction Summary [new2] / Treatment of Concept: [new2A]
Indication: Hyperphenylalaninaemia (HPA) due to phenylketonuria (PKU)
Treatment Phase: Maintenance treatment
Clinical criteria:
~~Patient must have previously received PBS-subsidised treatment under the Initial treatment (induction, titration, and maintenance) restriction with this drug for this condition~~ *Patient must have previously received PBS-subsidised treatment under the Initial treatment restriction with this drug for this condition,*
AND
Clinical criteria:
~~Patient must have demonstrated a response to initial treatment with this drug, assessed at a minimum of a minimum of 21 weeks and up to 24 months from commencing treatment with this drug, 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~~ *Patient must have demonstrated a response to initial treatment with this drug, defined as a blood phenylalanine level below 360 micromole per L*
AND
Clinical criteria:
Patient must be undergoing regular phenylalanine testing and assessment of adherence to dietary modifications
AND
Clinical criteria:
The treatment must not be in combination with sapropterin
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.~~ *Must be treated by a health practitioner who is any of (i) a medical practitioner, (ii) a nurse practitioner in consultation with a metabolic physician*
Prescribing Instructions: ~~At the time of the authority application, prescribers should request the appropriate quantity of prefilled syringes, required to provide 6 months of treatment at a dose of 60 mg per day or the patient's maximum tolerated dose.~~ *At the time of authority application, prescribers must request the appropriate strength(s) and number of prefilled syringes, to provide sufficient drug for 1 month of treatment at the dosage regimen specified in the approved Therapeutic Goods Administration (TGA) Product Information (PI). A separate authority prescription form must be completed for each strength requested.* ***The maximum listed quantity** or number of repeats **must not be prescribed** if lesser quantity or repeats are sufficient for the patient's needs.*
Prescribing Instructions: Blood phenylalanine levels must be based on measurements taken during stable periods of the condition.
Prescribing Instructions: Dietary phenylalanine intake must be maintained at a constant level

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. In adults, untreated high Phe-blood levels can cause neuropsychiatric symptoms including inattention, hyperactivity, anxiety, depression, seizures and tremors, and can impact executive function. This can have negative impacts on a person's employment and relationships, as well as their ability to appropriately manage their PKU.

4.2 The PBAC 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 issues with mental development, neurocognitive deficits, behavioural abnormalities, seizures and other serious neurological complications (paragraphs 4.2, 7.1 and 7.3, p29 sapropterin March 2018 PSD). 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).

4.3 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 impacts through neuropsychiatric symptoms and executive functioning impacts, but also through the negative impacts of a Phe-restricted diet. 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.

4.4 While pegvaliase substitutes for the deficient PAH enzyme, sapropterin is a cofactor for PAH and is dependent on residual PAH efficiency, with patients who are most likely to respond to sapropterin those with lower baseline Phe levels and 'milder' disease. The resubmission stated that as pegvaliase is an enzyme substitution therapy with pharmacological activity independent of BH4, there is not expected to be a relationship between a patient's historical response to sapropterin and the efficacy of pegvaliase.

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

5 Comparator

5.1 As in the previous pegvaliase submission, the resubmission proposed Phe-restricted diet alone as the comparator.

5.2 The resubmission stated that as the proposed population are non-responders to sapropterin and there are no other available pharmacological treatments for PKU, the comparator is a Phe-restricted diet alone. The resubmission did not provide any justification as to why a Phe-restricted diet alone is an appropriate comparator for the proposed population of patients who have responded to sapropterin but have protein tolerance of less than 15 g/day.

5.3 For the July 2022 submission, 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 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 (paragraph 7.6 PSD July 2022 PBAC meeting).

5.4 The PBAC previously 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 (paragraph 7.14, pegvaliase PSD, July 2022 PBAC meeting). Despite this, the resubmission maintained a requested listing among sapropterin non-responders and thus did not propose sapropterin as a comparator. Consequently, the resubmission did not provide any data comparing pegvaliase versus sapropterin in the proposed patient population. While this may be appropriate for patients who did not respond to sapropterin, the evaluation considered that sapropterin would provide an appropriate comparator for the additional proposed

patient population who have responded to sapropterin. These patients are likely to be receiving sapropterin but may have the option to switch to pegvaliase if they meet the proposed criteria of having a daily protein tolerance of less than 15 grams.

5.5 Sapropterin is currently PBS-listed for the treatment of HPA due to PKU where:

- For initial treatment, the patient must have a baseline blood Phe level > 360 µmole/L if less than one month of age or a baseline blood Phe level > 600 µmole/L if more than one month of age; and
- Initial responsiveness testing is for a period of 24 hours in a patient less than one month of age or for a period of 7 days in a patient aged more than one month.
- Continuing treatment criteria: During initial responsiveness testing, patient must have ≥ 30% reduction in Phe from baseline.
- Initial treatment must be by a metabolic physician. Continuing treatment can be by a metabolic physician or nurse practitioner.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The sponsor highlighted the significant unmet need for this patient group and the stakeholder support for listing in the requested population as opposed to the current situation of no access to pegvaliase at all. Further, the sponsor reiterated its commitment to working with the PBAC to implement its proposed RSA or an alternative mechanism that balances the PBAC's concerns and commercial constraints.

Consumer input

6.2 The PBAC noted and welcomed the input from individuals (11), carers (36), other interested individuals (8) and an organisation, via the Office of Health Technology Assessment Consultation Hub. The input described the challenges of living with PKU including the significant impact of dietary restrictions, including the social, emotional and practical burden of these restrictions. The input also outlined the cognitive impacts of high Phe levels including difficulty concentrating, reduced mental clarity, anxiety and fatigue. Carers, parents and partners of patients expressed concerns about long-term cognitive damage.

6.3 Patients described current care, including sapropterin, as only providing partial metabolic control. Some patients described sapropterin as having some benefit but that significant dietary restrictions are still required. The comments described pegvaliase as being 'transformative' and outlined a hope that pegvaliase would be

more effective than existing therapies, allowing less-strict dietary restrictions and improved cognitive function. Families outlined the fear of long-term neurological harm with PKU and viewed pegvaliase as a pathway to protecting long-term brain health. Safety concerns with pegvaliase were acknowledged (i.e. possible anaphylaxis, immune responses, and daily injections) but these were seen as manageable with the benefits outweighing the risks. The PBAC considered that, based on the consumer input, there remains a high unmet need for better treatments of PKU.

6.4 Five clinicians or groups specialising in metabolic conditions (nominated by MDAA) provided input about specific issues ahead of PBAC consideration.

- The respondents supported including the group of patients with protein tolerance < 15 g per day who meet the PBS sapropterin response criterion (≥ 30% reduction in blood Phe) with all indicating this would not be considered an adequate response in clinical practice. The respondents advised that this group is unlikely to materially impact the number of patients treated given most of this group have classical PKU and are unlikely to meet the PBS sapropterin response criteria. Most respondents indicated that 'daily protein tolerance' could be quantified (it may require dietician input) but one said it may be challenging to quantify given it usually involves 'trial and error'.
- For the response assessment timeframe, three respondents indicated that 24 months (as proposed in the submission) would be appropriate; though one preferred a staged approach with: (1) early response assessment at 16 to 24 weeks; (2) primary assessment at 52 weeks based on multiple measurements; and (3) an assessment at 24 months for 'slow responders'. The respondents all considered that response should be based on Phe levels with most considering these should be measured over a series of time (e.g. 4 samples in a one month period with < 360 µmol/L). All respondents considered there was no role for ADHD scores in response assessment given these are not validated.
- With regard to nurse practitioner prescribing, three respondents advised that nurse practitioners should not initiate prescribing because of the potential for 'significant' reactions with pegvaliase, though one suggested a shared-care model with physician involvement in initiation, and one respondent strongly advocated for nurse practitioner prescribing given the lack of paediatric metabolic physicians.
- Views on access to adrenaline injections were mixed. As outlined in paragraph 3.16, the PSCR stated "all metabolic physicians consult with relevant specialists (i.e., paediatrician, clinical immunologist, allergist, or respiratory physician) and provide their name at the time of the initial Authority Required Application for PBS supply of an adrenaline injection device". Two of the five respondents indicated this was feasible and two said it would be difficult or not possible to consult with appropriate clinicians to enable access to adrenaline auto-injector devices. Three respondents suggested broadening access to adrenaline auto-injector devices (e.g. include metabolic physicians).

- All respondents supported allowing patients to switch back to sapropterin. Some of the respondents noted that sepiapterin may be a potential future option.

Clinical studies and trials

6.5 As in the previous submission, the efficacy and safety of pegvaliase continued to be informed by PRISM 1 and PRISM 2. As in the previous submission, the resubmission was based on a matched-adjusted historical cohort analysis (Zori 2019) and a naïve-indirect comparison, both using:

- pegvaliase patient data from (a) one randomised trial which included one eight-week component that compared pegvaliase to placebo (PRISM 2) and (b) one randomised trial comparing pegvaliase 20mg/day to pegvaliase 40mg/day (PRISM 1); and
- data from the Phenylketonuria PKU Demographics, Outcomes and Safety (PKUDOS) study to inform outcomes in patients treated with Phe-restricted diet alone, after previously being treated with sapropterin.

For the previous submission, the ESC considered that a key underlying issue with these comparisons was that neither included a common comparator arm (paragraph 6.23, pegvaliase PSD, July 2022).

6.6 The resubmission presented an additional unanchored comparison of pegvaliase-treated and Phe-restricted diet alone-treated patients (Burton 2024). This analysis used data from the same trials/studies (PRISM vs PKUDOS), with the primary difference (compared to analyses previously considered by the PBAC) being the use of quantile regression and the availability of a longer follow-up period (three years).

6.7 Details of the trials and studies presented in the resubmission are provided in Table 3. These publications are the same as those previously evaluated by the PBAC for pegvaliase in July 2022, with the addition of the publications Rohr 2024 and Burton 2024. While Rohr 2024 was listed as an additional publication for the PRISM 2 trial, the resubmission did not present any data from this source.

Table 3: Trials, studies and associated reports presented in the resubmission

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
	Rohr, F. et al., 2024. Evaluating change in diet with pegvaliase treatment in adults with phenylketonuria: analysis of phase 3 clinical trial data.	Mol Genet Metab. 2024; 143(4):108613
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
Quantile regression analysis	Burton, B. et al. Long-term comparative effectiveness of pegvaliase versus medical nutrition therapy with and without sapropterin in adults with phenylketonuria.	Mol Genet Metab. 2024; 141(1):108114

Note: Blue shading indicates data previously considered by the PBAC.
Source: Table 2.2-2, pp65-66 of the resubmission.

6.8 The key features of the included evidence are summarised in Table 4.

Table 4: 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	Blood-Phe; Dietary Phe intake; Psychiatric assessment; Safety	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	Patients who completed PRISM 2 Part 2	As above; Pharmacodynamics	
Pegvaliase vs placebo						
PRISM 2 Part 2	95	R, DB, MC 8 weeks	High [a]	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 [b]	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
Burton 2024	382 [c]	Quantile regression analysis	High [b]	PRISM patients; PKUDOS patients; baseline blood-Phe ≥600 µmol/L; ≥16 years old	Blood-Phe; protein intake; Phe response rate	No
Indirect naïve comparison	311	Indirect naïve comparison	High [d]	PRISM patients; PKUDOS patients aged≥18, previously treated with sapropterin, >600µmol/L	Blood-Phe; Phe response rate	Yes (blood-Phe)

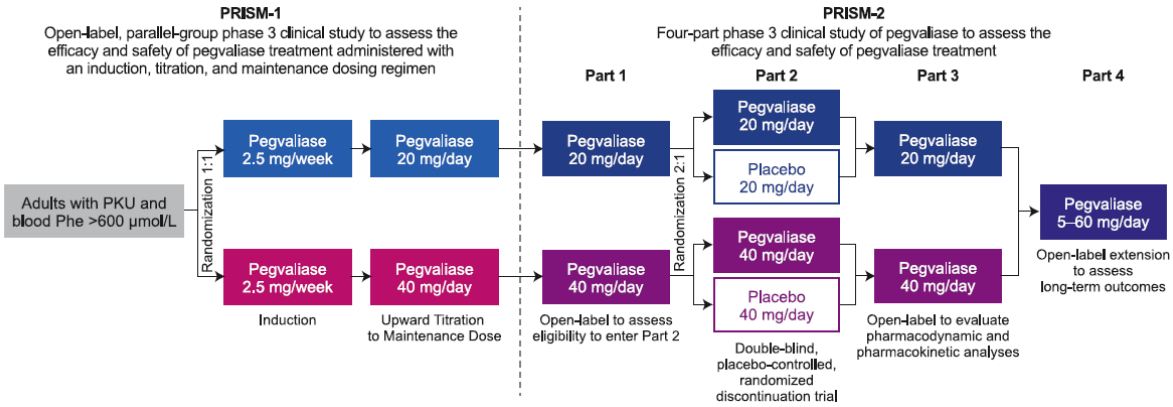
Note: Blue shading indicates data previously considered by the PBAC.
Source: Table 3, pegvaliase PSD, July 2022 PBAC meeting; Section 2 of the resubmission.
DB = double blind; MC = multi-centre; NA = not applicable; OL = open label; Phe = phenylalanine; R = randomised.
[a] High risk of selection bias as only patients who achieved a ≥20% reduction in blood-Phe from pegvaliase-naïve baseline were included
[b] 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.
[c] While the resubmission only used the pegvaliase (n = 183) and Phe-restricted diet only (n = 67) arms, the analysis by Buton et al. (2024) also included patients who received sapropterin + Phe-restricted diet (n = 82).

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

6.9 For the previous submission, all evidence was considered to have a high risk of bias (Table 3, pegvaliase PSD, July 2022 PBAC meeting). Burton 2024 was considered to have a high risk of bias during the evaluation, predominantly due to confounding due to the use of data from two studies/trials that had no common comparator arm, a high risk of selection bias and potential bias due to missing data for PRISM and PKUDOS.

6.10 As previously noted by the PBAC, 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 2. 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.

Figure 2: PRISM 1 and PRISM 2 trial study designs



Source: Figure 2.3-1 (p69) of the submission
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.
The evaluation and ESC previously considered that PRISM 2 Part 2 was associated with a high risk of selection bias as only patients who achieved a ≥ 20% reduction in blood-Phe from pegvaliase-naïve baseline were included, favouring pegvaliase. Further, the ESC previously 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 (paragraph 6.20, pegvaliase PSD, July 2022 PBAC meeting).

6.11 PKUDOS was a Phase 4 voluntary observational multi-centre registry study that included PKU patients who had previously received sapropterin therapy, were currently receiving sapropterin therapy or intended to receive sapropterin therapy. As noted by the PBAC for the previous submission, PKUDOS included patients who had discontinued sapropterin for any reason and the reasons for discontinuation were not reported in the (re)submission. It was unknown if these patients were sapropterin responders (as defined in the requested restriction), so the applicability of these data were unclear. Previously, 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 (paragraph 6.21, pegvaliase PSD, July 2022 PBAC meeting).

6.12 The resubmission presented three unanchored indirect comparisons of pegvaliase versus a Phe-restricted diet alone using various cohorts of the PRISM and PKUDOS studies, and different statistical methodology:

- Zori 2019 reported an indirect matched analysis that selected patients for the pegvaliase arm (n = 125) from either the Phase 2 165-205 study (24-week, single-arm, open-label dose-optimisation study that allowed pegvaliase doses of between 2.5mg per week up to 375 mg five times per week; enrolled patients were eligible to enrol in PRISM 2) or the PRISM trials (pegvaliase dose 5 to 60 mg/day). To be included in the Phe-restricted diet alone group from PKUDOS, patients must have previously received sapropterin (n = 64). This study also included a sapropterin plus diet arm based on patients from PKUDOS. Propensity scores were estimated using logistic regression with probability of treatment as outcome (i.e. pegvaliase, "sapropterin + diet", or "diet alone") and patient demographic and disease severity covariates (baseline age, gender, baseline blood Phe concentration and baseline dietary Phe) as predictors.
- An indirect comparison was conducted to inform the July 2022 pegvaliase submission that investigated the proportion of patients who achieved blood-Phe ≤ 360 µmol/L, ≤ 600 µmol/L and reduction of ≥ 30% from baseline. The pegvaliase arm included patients from PRISM 1 (n = 261) and the Phe-restricted diet population included patients from PKUDOS (n = 50) aged ≥ 18 years-old who were previously treated with sapropterin and had a post-sapropterin blood-Phe (defined as between 28 to 90 days post-sapropterin) of > 600 µmol/L.
- Burton 2024 was a quantile regression analysis that modelled median blood Phe response, adjusting for age, sex, and baseline blood Phe level at each time point. The study included patients aged ≥ 16 years with PKU who had baseline blood Phe concentrations > 600 µmol/L (PRISM; n= 183) or were not being treated with sapropterin and had blood Phe measurements available at baseline and at any of the 12- , 18-, 24-, and 36-month time points (PKUDOS; n = 82). This study also included a sapropterin plus diet arm. As noted for the studies previously evaluated by the PBAC, a key underlying issue for Burton 2024 is that it did not include a common comparator arm.

Comparative effectiveness

PRISM 1, PRISM 2 and PKUDOS

6.13 The results for PRISM 1, PRISM 2 and PKUDOS presented in the resubmission were identical to the results presented in the previous submission. While the resubmission requested listing for an additional patient population (those who have a daily protein tolerance < 15 g per day), the resubmission acknowledged there was no specific clinical evidence for the additional cohort.

6.14 The results for change in blood-Phe over time for the randomised, double-blind, placebo-controlled segment of PRISM 2 (Part 2) are presented in Table 5.

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) [a] N = 14	Placebo (40 mg/day pegvaliase previously in Part 1) [a] N = 14
Responder (blood-Phe ≤ 360µmol/L) [b]			
n/N (%)	25/49 (51)	0/13 (0)	0/10 (0)
Phe levels (µmol/L), Mean (SD)			
Baseline[c]	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[d]	-638.27 (-858.97, -417.57) p < 0.0001[d]

Note: This data has previously been reviewed by the PBAC.
Source: Table 2.5-5, p129 of the resubmission, Table 14.2.8.1.230, p3372 165-302 PRISM 2 CSR
CI = confidence interval; LS = least squares; mITT = modified intention-to-treat; MMRM = mixed-model repeated measures; Phe = phenylalanine; SD = standard deviation
[a] 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.
[b] It was unclear why there were missing data from the responder analysis.
[c] 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).
[d] 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.

6.15 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. As noted for the previous submission, this was inconsistent with the assumptions applied in the economic model. However, the PBAC previously 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 previously 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 previously considered that the treatment effect may have been overestimated due to the drop out of patients with poor response to pegvaliase (paragraph 6.25, pegvaliase PSD, July 2022 PBAC meeting).

6.16 The PBAC previously observed that patients treated with pegvaliase in PRISM 1 and 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. 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 (paragraph 6.27, pegvaliase PSD, July 2022 PBAC meeting).

6.17 The PBAC previously noted that the results for the previously treated group in PKUDOS show a slight decrease in blood-Phe over time, however standard deviations (SDs), around the estimate are large and over-lapping, and therefore there is a large amount of uncertainty in the results (paragraph 6.28, pegvaliase PSD, July 2022 PBAC meeting).

Indirect comparisons: pegvaliase vs Phe-restricted diet

6.18 An overview of the results for the common outcomes of patients achieving blood Phe levels ≤ 360 µmol/L and ≥ 30% reduction from baseline at Years 1 and 2 for Zori 2019 and the naïve indirect comparison and Burton 2024 are shown in Table 6.

Table 6: Blood-Phe level outcome results over time in the Zori 2019, the indirect analysis and Burton 2024

	≤ 360 µmol/L			≥ 30% reduction from baseline		
	Pegvaliase n/N (%)	**Phe-restricted diet n/N (%)**	**OR (95% CI)**	**Pegvaliase n/N (%)**	**Phe-restricted diet n/N (%)**	**OR (95% CI)**
Year 1						
Zori 2019	41/87 (47)	0/51 (0)	NC	58/87 (67)	9/51 (18)	**0.11 (0.05, 0.25)**
Indirect analysis[a,b]	96/261 (37)	4/50 (8)	**0.15 (0.05, 0.43)**	147/261 (56)	9/50 (18)	**0.17 (0.08, 0.36)**
Burton 2024	13/180 (7)	0/42	NC	NR	NR	NR
Year 2						
Zori 2019	58/80 (72)	1/42 (2)	**0.01 (0.00, 0.07)**	65/80 (81)	9/42 (21)	**0.06 (0.02, 0.16)**
Indirect analysis [b]	135/261 (52)	3/50 (6)	**0.06 (0.02, 0.20)**	169/261 (65)	13/50 (26)	**0.19 (0.10, 0.38)**
Burton 2024	79/165 (48)	0/32	NC	NR	NR	NR

Note: Blue shading indicates data sets previously considered by the PBAC. Bold denotes a statistically significant value (p ≤ 0.05)
Source: Tables 2.6-3, 2.6-10 and 2.6-12 and Figure 2.6-3, pp 166, 172, 186 and 189 of the resubmission; evaluator conducted calculations.
CI = confidence interval; NC = not calculable; NR = not reported; OR = odds ratio; Phe = phenylalanine
[a] Year 1 results were for 7 to 12 months.
[b] In the resubmission, data for the indirect comparison was amended to calculate response rates using the total baseline samples size as the denominator, instead of the number of patients at risk at a particular time. Therefore, while the dataset for the indirect analysis has previously been reviewed by the PBAC, the figures shown have been modified compared to the results presented in the previous submission.

6.19 As in the previous submission, the resubmission presented responder analyses results for blood Phe-level outcomes over time from Zori 2019. Zori et al. (2019) reported that

matched patients treated with pegvaliase achieved better results across all blood-Phe outcomes than patients treated with Phe-restricted diet. For the 2022 submission, the evaluation and the ESC previously noted the following issues with the analysis by Zori et al (2019):

- 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.
- 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 (paragraph 6.30, pegvaliase PSD, July 2022 PBAC meeting).

6.20 The resubmission presented results for a naïve indirect comparison that found the patients treated with pegvaliase achieved higher responder rates than patients treated with Phe-restricted diet. Refer to Table 7 for details of the responder analysis for blood-Phe level ≤ 360 µmol/L. As in the previous submission, the resubmission presented observed data using the number of patients at risk as the denominator, however the resubmission also presented data calculated using the total sample size.

Table 7: Blood-Phe level response (≤ 360 µmol/L) over time in the indirect comparison

Time period	Observed data			Based on total baseline sample size		
	Pegvaliase n (%)	Phe-restricted diet n (%)	OR (95% CI)	Pegvaliase N = 261 n (%)	Phe-restricted diet, N = 50 n (%)	OR (95% CI)
Baseline	n = 261 0 (0)	n = 50 0 (0)	-	0 (0)	0 (0)	-
1-6 months	n = 257 70 (27)	n = 37 6 (16)	*0.52 (0.21, 1.29)*	70 (27)	6 (12)	***0.37 (0.15, 0.91)***
7-12 months	n = 209 96 (46)	n = 32 4 (13)	***0.19 (0.06, 0.50)***	96 (37)	4 (8)	***0.15 (0.05, 0.43)***
Year 2	n = 186 [a] 135 (73)	n = 27 3 (11)	**0.06 (0.01, 0.16)**	135 (52)	3 (6)	***0.06 (0.02, 0.20)***
Year 3	n = 162 139 (86)	n = 21 2 (10)	***0.02 (0.00, 0.08)***	139 (53)	2 (4)	***0.04 (0.01, 0.15)***
Year 4	n = 132 112 (85)	n = 13 2 (15)	***0.04 (0.01, 0.18)***	112 (43)	2 (4)	***0.06 (0.01, 0.23)***
Year 5	n = 74 58 (78)	n = 11 0 (0)	*NE*	58 (22)	0 (0)	*NE*

Note: This data set has previously been reviewed by the PBAC; however, the resubmission additionally presented this data to include response rates using the total baseline samples size as the denominator.
Bold denotes a statistically significant value (p ≤ 0.05). Blue shading indicates data sets previously seen by the PBAC.
Source: Table 2.6-12, p 189 of the resubmission; evaluator conducted calculations in italics.
CI = confidence interval; NE = not estimable; OR = odds ratio; Phe = phenylalanine
[a] 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.

6.21 The economic model relied on pegvaliase responder rates from the naïve indirect comparison, as was the case for the previous pegvaliase submission. The resubmission did not provide any justification as to why these data were used to inform the economic evaluation rather than data from Zori 2019 or Burton 2024. While the resubmission presented amended response rates incorporating the total baseline sample size as the denominator (rather than using the number of patients at risk at a particular time as in the previous submission), the pegvaliase response rate used in the economic model was not updated. As in the 2022 economic model, a pegvaliase response rate of 81.8% (135/165) was used based on the further exclusion of 21 patients who did not remain on pegvaliase for two years.

6.22 The analysis calculated that 14 of the remaining 30 patients (who were not considered pegvaliase responders based on Phe blood) achieved at least one recorded score of a ≥ 5 ADHD-RS inattention subscale score reduction within the two years, representing 8.5% (14/165). These responder values (81.8% + 8.5% = 90.3%) were applied in the economic model.

6.23 Comparatively, a 0% response rate was assumed in the economic model for Phe restricted diet only patients. As noted for the previous submission (paragraph 6.35, pegvaliase PSD, July 2022 PBAC meeting), this was not supported by the PKUDOS data which reported an up to 16% blood-Phe response rate at 6 months using the 2022 submission's calculation methods (12% using the total baseline samples size as the

denominator as presented in the resubmission). This favoured pegvaliase in the economic model.

6.24 Burton 2024 reported results for blood Phe at baseline and at 1, 2, and 3 years of follow-up for pegvaliase from the PRISM trials and Phe-restricted diet alone in PKUDOS, as summarised in Table 8.

Table 8: Burton 2024 clinical outcomes with pegvaliase and Phe-restricted diet alone at baseline and 1, 2, and 3 years of follow-up (observed data)

	Pegvaliase (N = 183)			
	Baseline	**Year 1**	**Year 2**	**Year 3**
Blood Phe, µmol/L				
n	183	180	165	153
Mean (SD)	1258.0 (365.3)	605.7 (556.2)	400.2 (514.3)	396.9 (463.6)
Median (IQR)	1244.0 (984.5–1508.5)	535.0 (34.8-1,065.3)	142.0 (6.0-735.0)	167.0 (9.0-763.0)
MAD	416.4	624.8	525.2	491.5
Protein intake from natural food (g/day)[a]				
n	176	174	160	146
Mean (SD)	39.2 (27.9)	48.0 (28.5)	58.0 (28.1)	63.3 (27.8)
Median (min, max)	30.4 (4.2, 155.3)	39.3 (6.9, 128.8)	56.7 (7.0, 127.8)	63.5 (7.1, 126.0)
	Phe-restricted diet alone (N = 67)			
	Baseline	**Year 1**	**Year 2**	**Year 3**
Blood Phe, µmol/L				
n	67	42	32	27
Mean (SD)	1,082.0 (298.6)	963.4 (315.8)	940.9 (388.3)	1,134.0 (523.6)
Median (IQR)	984.0 (846.5–1368.5)	939.0 (675.5-1,149.0)	941.1 (671.0-1,225.2)	1,157.0 (727.2-1,470.0)
MAD	342.8	364.9	446.5	605.3
Protein intake from natural food (g/day) [a]				
n	47	14	10	4
Mean (SD)	20.4 (17.5)	23.9 (16.6)	16.5 (11.3)	22.9 (10.1)
Median (min, max)	14.0 (3.0, 74.9)	19.0 (4.0, 69.5)	12.6 (3.6, 39.6)	24.0 (10.5, 33.0)

Source: Table 2.6-6, p170 of the resubmission

IQR = interquartile range; MAD = mean absolute difference; max = maximum; min = minimum; Phe = phenylalanine; PKUDOS = Phenylketonuria Demographics, Outcomes and Safety Registry; SD = standard deviation.

[a] For the pegvaliase group: intact protein intake = average dietary protein intake from intact food (g/day); for Phe-restricted diet alone group: intact protein intake (g/day) = total protein intake – medical food protein intake. Calculated intact protein intake measures of <0 g/day and ≥200 g/day were excluded due to the improbability that the measurement was correct.

6.25 The results for Burton 2024 indicated that for patients treated with pegvaliase, blood-Phe was reduced over time to a greater extent than for patients treated with Phe-restricted diet, and protein intake was increased over time to a greater extent than for patients treated with Phe-restricted diet. However, there was a high level of uncertainty in the clinical evidence and comparative effectiveness because:

- The study was associated with a high risk of bias, predominantly due to confounding due to the use of data from two studies/trials that had no common comparator arm, a high risk of selection bias and potential bias due to missing data for PRISM and PKUDOS.
- There were differences in baseline characteristics between the treatment groups. Baseline blood Phe levels were higher in pegvaliase-treated patients (median:

1,244.0 µmol/L) compared with the Phe-restricted diet alone patients (median: 984.0 µmol/L). Similarly, baseline protein intake was higher in the pegvaliase-treated patients (median: 30.4 g/day) compared with the Phe-restricted diet alone patients (median: 14.0 g/day). It was unclear if these differences were due to actual differences between the patient populations or if this was a consequence of the patient populations being sourced from different studies/trials with no common comparator.

- While the analysis adjusted for age, sex, and baseline blood Phe concentrations at each time point, it was unclear whether all relevant effect modifiers and prognostic variables were adjusted for in the analysis.
- While the Phe-restricted diet arm initially included 67 patients, results for considerably fewer patients were available over time for both the blood Phe and protein intake outcomes but most notably for the protein intake outcome. This is likely to have limited the robustness of this data and its comparison with the pegvaliase group.
- For the pegvaliase group, the blood-Phe level results have large SDs. This suggests a sizeable amount of uncertainty is associated with these results.

Consequently, the results from Burton 2024 appear unable to robustly inform the magnitude of the incremental benefit that could not be reliably estimated in the previous pegvaliase submission (paragraph 7.8, pegvaliase PSD, July 2022 PBAC meeting).

Other comparative effectiveness data

6.26 As observed for the previous submission, 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). The PBAC noted that both treatments led to decreases in blood-Phe over time, but compared to sapropterin, a higher proportion of patients treated with pegvaliase achieved ≤ 360 µmol/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 (paragraph 6.31, pegvaliase PSD, July 2022 PBAC meeting).

6.27 While not discussed in the resubmission, the study by Burton 2024 included a treatment arm for patients who received sapropterin + Phe-restricted diet. A comparison was therefore made between patients treated with pegvaliase from the PRISM trials (n = 183) and patients treated with sapropterin + Phe-restricted diet from PKUDOS (n=82). While there were notable differences in baseline Phe levels (mean: pegvaliase = 1258.0 µmol/L, sapropterin + Phe-restricted diet = 989.9 µmol/L), the pegvaliase arm reported lower blood Phe at all time points (mean: year 1 605.7 µmol/L vs 690.6 µmol/L; year 2 400.2 µmol/L vs 659.6 µmol/L; year 3 396.9 µmol/L vs 693.0

µmol/L). The model-estimated proportions of patients achieving blood Phe ≤ 360 µmol/L using quantile regression (adjusting for age, sex, and baseline blood Phe level at each time point) was higher for patients treated with sapropterin + Phe-restricted diet in Year 1 (18% vs 9%) but was higher for patients treated with pegvaliase in Year 2 (96% vs 0) and Year 3 (84% vs 3%). While trials that have been conducted to specifically evaluate the efficacy of sapropterin were available to the sponsor (e.g. PKU-001, PKU-003, PKU-004, PKU-008 as evaluated by the PBAC in July 2022), Burton 2024 used registry data from PKUDOS to demonstrate the efficacy of sapropterin + Phe-restricted diet. The evaluation therefore considered it was unclear if this comparison of pegvaliase versus sapropterin + Phe-restricted diet was reasonable.

6.28 As in the previous submission, the resubmission presented an analysis of PRISM subgroup results by sapropterin responder status. The PBAC previously noted that limited exploratory subgroup analyses suggested that sapropterin responder-status was not a treatment effect modifier (paragraph 7.4, pegvaliase PSD, July 2022 PBAC meeting).

6.29 As in the previous submission, the resubmission 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. The PBAC previously considered that the supportive evidence from the literature suggested 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 as 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 (paragraph 7.9, pegvaliase PSD, July 2022 PBAC meeting).

6.30 As in the previous submission, the resubmission presented neurocognitive/psychiatric outcome data for the ADHD-RS inattention subscale from the PRISM trials. (As noted for the previous submission, the 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-RS inattention subscale scores as assumed by the submission in the economic model (paragraph 6.38, pegvaliase PSD, July 2022 PBAC meeting).

Comparative harms

6.31 Identical safety data was presented in the previous submission and the resubmission. Burton 2024 did not report any safety outcome data.

6.32 The safety results for patients treated with pegvaliase and placebo from PRISM 2 Part 2 are presented in Table 9.

Table 9: 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 [a]	
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 [b]	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)

Note: This data has previously been reviewed by the PBAC.
Source: Table 2.5-14, p145-146 of the resubmission; Table 11, pegvaliase PSD, July 2022.
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
[a] Patients in Part 2 placebo group received 4.4 person-years of exposure to placebo
[b] 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.

6.33 For the previous submission, the PBAC noted that the results from PRISM 2 Part 2 indicate that patients treated with pegvaliase had a higher incidence of hypersensitivity (risk difference [RD] = 0.26, 95% confidence interval [CI] 0.09, 0.43) and generalised skin reactions lasting longer than 14 days (RD = 0.11, 95%CI 0.03, 0.19), and that in clinical practice, patients would not receive placebo injections and therefore it is expected that injection site reactions would be more frequent with pegvaliase. The PBAC also noted that as PRISM 2 Part 2 only treated patients for eight weeks, the comparative safety over a longer treatment period was unknown (paragraph 6.45, pegvaliase PSD, July 2022 PBAC meeting).

6.34 Hypersensitivity reactions were very common, although most of these were mild to moderate. The pegvaliase PI states that acute systemic hypersensitivity reaction has been reported after administration of pegvaliase and may occur at any stage during treatment. The PBAC previously 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 adverse event (AE) rates in Table 9, particularly hypersensitivity AE and generalised skin reaction, are likely to underestimate the true burden of AEs for pegvaliase (paragraph 6.46, pegvaliase PSD, July 2022 PBAC meeting).

Benefits/harms

6.35 As the efficacy and safety data for PRISM 2 Part 2 remained the same as in the previous submission and no additional randomised controlled trial data were presented in the resubmission, the benefits/harms of pegvaliase were unchanged. On the basis of direct evidence presented by the resubmission, for every 100 patients treated with pegvaliase plus Phe-restricted diet in comparison with Phe-restricted diet:

- Approximately 51 additional patients achieve a blood-Phe level of ≤ 360 µmol/L after eight weeks.
- Approximately 26 more patients would have a hypersensitivity adverse event.
- Approximately 11 more patients would have a generalised skin reaction lasting 14 or more days.

6.36 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

6.37 The evaluation considered that the following key issues, which were raised for the previous submission, remain applicable to the resubmission:

- The ESC previously 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). (paragraph 6.52, pegvaliase PSD, July 2022 PBAC meeting). The additional comparison provided in the resubmission (Burton 2024) had similar limitations in methodology as it also compared treatment with pegvaliase using data from PRISM versus a Phe-restricted diet using data from PKUDOS, without a common comparator arm.
- The PBAC previously 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 previously 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 ≥ 20% reduction in blood-Phe. As such the clinical data reflected patients who already had a degree

of responsiveness and tolerability to pegvaliase (paragraph 7.7, pegvaliase PSD, July 2022 PBAC meeting).

- The PBAC previously 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 (paragraph 7.8, pegvaliase PSD, July 2022 PBAC meeting).

6.38 The approach taken in the resubmission to support the clinical claim was the same as in the July 2022 submission with the addition of Burton 2024. The resubmission described pegvaliase as superior in terms of effectiveness compared to a Phe-restricted diet. While this claim may be adequately supported, the magnitude of the effect remained uncertain as Burton 2024 did not provide any data to allow the determination of the magnitude of the incremental benefit.

6.39 The PBAC previously advised that any resubmission should not restrict access based on prior response to sapropterin. Although this advice was partially adopted in the resubmission (i.e. inclusion of patients meeting the PBS responsiveness criteria, but with a protein tolerance of less than 15 grams per day), the resubmission did not follow the PBAC's advice that sapropterin should be included as a comparator in any resubmission (paragraph 7.14, pegvaliase PSD, July 2022 PBAC meeting). Consequently, while pegvaliase appears to be effective at reducing blood Phe levels when compared to a Phe-restricted diet, the effectiveness versus sapropterin remains unclear. The evaluation considered that sapropterin may be a particularly relevant comparator for the additional proposed population of sapropterin responders (protein intake ≤ 15 g/day), as these patients would likely discontinue sapropterin to initiate pegvaliase.

6.40 As in the previous submission, the resubmission described pegvaliase as inferior in terms of safety compared to a Phe-restricted diet. This claim was adequately supported. The PBAC previously 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 (paragraph 7.10, pegvaliase PSD, July 2022 PBAC meeting).

6.41 As for the efficacy outcomes, it remains unknown whether pegvaliase would have superior, inferior or non-inferior safety compared to sapropterin in the proposed patient population.

6.42 The PBAC considered that the claim of superior comparative effectiveness versus a Phe-restricted diet alone was reasonable, in terms of blood-Phe reduction.

6.43 The PBAC considered that the claim of inferior comparative safety versus a Phe-restricted diet alone was reasonable.

Economic analysis

6.44 The resubmission presented a stepped cost-utility analysis using a micro-simulation model to compare pegvaliase with a Phe restricted diet versus a Phe-restricted diet. While this was consistent with the clinical claim, the model did not incorporate the proposed population of patients with PKU aged 16 years and over who are responders to sapropterin and have a daily protein tolerance of less than 15 grams. Additionally, the economic evaluation did not allow any comparison of pegvaliase versus sapropterin, which the evaluation considered may be a relevant comparison in this proposed patient population of sapropterin responders.

6.45 The evidence informing effectiveness in the economic evaluation was based on two sequential Phase 3 trials (PRISM 1 and 2) to inform the pegvaliase intervention arm and based on assumptions and on a longitudinal registry dataset (PKUDOS) to inform the Phe-diet alone comparator arm. As in the 2022 pegvaliase submission, no direct comparative clinical data between the two treatment arms were used to inform the economic evaluation and this was a key source of uncertainty in the economic model.

6.46 The model structure, key inputs and rationale are described in Table 10. With the exception of the change to the assumed pegvaliase cost and some minor changes to the model inputs, the economic evaluation structure and inputs remained largely unchanged versus the July 2022 pegvaliase submission.

Table 10: Summary of model structure, key inputs and rationale

Component	Summary	Comments
Treatments	Pegvaliase plus a Phe-restricted diet vs a Phe-restricted diet alone	Unchanged. While this was consistent with the 2022 model it did not incorporate the proposed population of patients with PKU aged 16 years and over who are responders to sapropterin and have a daily protein tolerance of less than 15 grams and it did not include sapropterin as a comparator.
Type of analysis	Cost-utility analysis	Unchanged. Reasonable.
Outcomes	Responders and quality adjusted life years gained	Unchanged. Reasonable.
Methods used to generate results	Microsimulation model using @Risk and Microsoft Excel. Microsimulation was used to determine 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.	Unchanged. For the 2022 model, the ESC considered there was a lack of clinical data available to support the microsimulation approach undertaken. The use of a microsimulation model resulted in an unnecessarily complicated model, which required significant time to compute (paragraph 6.61, pegvaliase PSD, July 2022 PBAC meeting). While the PSCR for the July 2022 submission reiterated that a Markov model would be problematic, the ESC considered this justification was inadequate (paragraph 6.62, pegvaliase PSD, July 2022 PBAC meeting).
Time horizon	Lifetime (up to 100 years of age) in the model base-case vs 5 years in the key clinical studies	Unchanged. For the 2022 model, 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.

Component	Summary	Comments
Cycle length	1 week	Unchanged. This increases the computation complexity of the microsimulation with a life-time horizon.
Health states	'Responder', 'non-responder', 'Phe-restricted diet' and 'dead'. A responder was defined as achieving either blood Phe ≤ 360 µmol/L or ADHD-RS inattention subscale reduction of ≥ 5 from baseline by 2 years	Unchanged.
Transition probabilities	**Pegvaliase response rate**: Calculated from an analysis of February 2019 PRISM trial data-cut including patients with ≥ 2 years of pegvaliase treatment who achieved either ≤ 360 µmol/L (81.8%) or ADHD-RS inattention subscale reduction of ≥ 5 from baseline (8.5%). **Phe-diet alone response rate:** Assumed to be 0%.	As the pegvaliase response rate was based on the subset of patients who remained on pegvaliase for at least two years, a higher proportion of pegvaliase responders is likely to have been captured as non-responders were less likely to continue with treatment. As observed for the 2022 model, a 0% response rate was assumed in the model for Phe restricted diet only patients, which was not supported by the data which reported an up to 16% blood-Phe response rate at 6 months. This favoured pegvaliase in the economic model (paragraph 6.35, pegvaliase PSD, July 2-022 PBAC meeting).
	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. **Phe-diet alone blood-Phe level over time**: Estimated from an additional analysis of the PKUDOS registry dataset and applied as a 108 µmol/L reduction from baseline and assumed as constant thereafter.	Blood-Phe levels for patients can reduce within health states over time, with larger reductions for responders. This incorporates effectiveness in the model as utility values are mapped to blood-Phe level.
	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. **Phe-diet alone discontinuation rate**: Assumed to be 0%.	
	Overall survival: Gender and age adjusted general population mortality.	Overall survival was updated to reflect more recently available ABS lifetables.
Adverse events	**Pegvaliase AEs**: Calculated from the incidence of AEs ≥ Grade 3 that occurred in ≥ 1% of patients in PRISM 1 and applied it on cycle 1 of the model. The resubmission stated that the approach to estimating the incidence of AEs of grade ≥ 3 was revised for the resubmission because the risk of events declines as the duration of treatment increases. **Phe-diet alone AEs**: Assumed to be 0%.	The same AE data from PRISM-1 was used in the model, but the method used to apply this data was updated in the resubmission. The 2022 model AE calculations included a cycle risk calculated from the incidence of AEs ≥ Grade 3 that occurred in ≥ 1% of patients in PRISM 1. The PBAC considered that these AE rates are likely to underestimate the true burden of AEs for pegvaliase (paragraph 7.10, pegvaliase PSD, July 2-022 PBAC meeting). As the same data was used, AEs were likely to continue to be underestimated, thereby favouring pegvaliase.

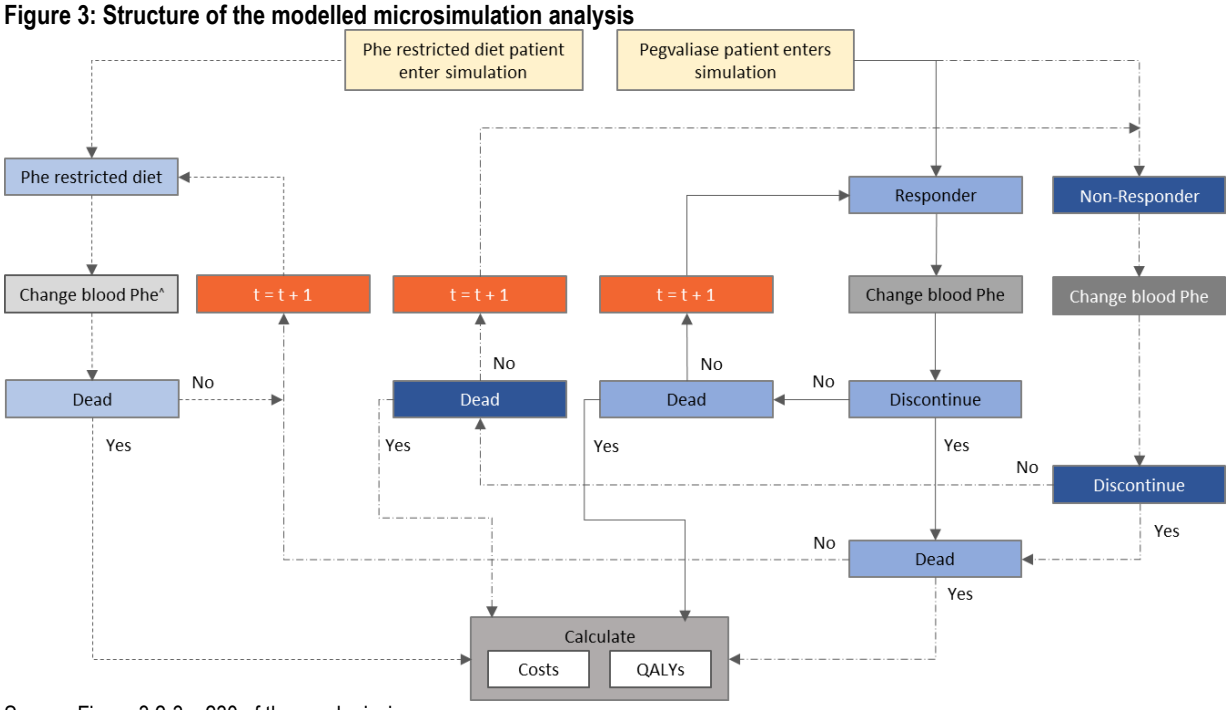
Component	Summary	Comments
Health related quality of life	TTO direct elicitation with Swedish general population preference weights. Utility values for health states from the utility study were applied to blood-Phe categories assumed by the resubmission to correspond to the given health states.	Unchanged. Previously, 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 (paragraph 6.71, pegvaliase PSD, July 2022 PBAC meeting).
Pegvaliase use and cost	Mean pegvaliase dose assumed to be 24.5 mg/day estimated from an analysis of the sponsor's database associated with the pegvaliase Risk Evaluation and Mitigation Strategy program.	The 2022 model used a mean pegvaliase dose of 30.5 mg/day based on PRISM data. The PBAC noted this was underestimated compared with clinical practice (paragraph 7.11, pegvaliase PSD, July 2022 PBAC meeting).
Pegvaliase cost	Assumed cost = $[redacted] per syringe.	The resubmission's base case model included the assumed pegvaliase cost based on the proposed RSA [redacted] Commonwealth expenditure caps. [redacted] The proposed AEMP was $[redacted] in the previous submission.
Other resource use and costs	All PBS, MBS and NHCDC AR-DRG costs were updated to include current values as of October 2025.	Generally reasonable. However, it was unclear why some MBS items fees were used with a 75% benefit (specialist and blood Phe testing) and an 85% benefit was used for dietician visits, which was inconsistent with the financial estimates where an 80% MBS rebate was applied. However, using an 80% rebate for all items had no impact on the ICER.

Source: Table 3.1-1, pp 208-210 of the resubmission.

ABS = Australian Bureau of Statistics; ADHD-RS = Attention-deficit hyperactivity disorder; ADHD-RS = Attention-deficit hyperactivity disorder rating scale; AE = adverse event; AEMP = Approved Ex-Manufacturer Price; NHCDC AR-DRG = National Hospital Cost Data Collection Australian Refined Diagnostic Related Groups; Phe = phenylalanine; PKU = phenylketonuria; TTO = time trade off

6.47 Figure 3 presents the model structure used in the economic analysis. The resubmission stated that the cohort simulation model as well as the approach to modelling changes in blood Phe over time and the associated quality of life (QoL) and cost impacts remain unchanged in the resubmission.

Figure 3: Structure of the modelled microsimulation analysis



Source: Figure 3.2-3, p230 of the resubmission
t = time; QALYs = quality adjusted life years
^ Patients treated with a Phe restricted diet were assumed to undergo a one-off reduction in blood Phe of 108 µmol/L at the end of the first model cycle with no further changes in subsequent cycles. The blood Phe level for patients who discontinue treatment with pegvaliase returns to baseline minus 108 µmol/L representing the impact of Phe restricted diet alone in the cycle after treatment discontinuation.

6.48 The model did not include any consideration of the additional patient population proposed in the resubmission (patients who are sapropterin responders having a protein tolerance of less than 15 g per day). The resubmission claimed that "Most patients in this additional cohort are expected to be eligible for pegvaliase under the proposed restriction as sapropterin non-responders but a small number of patients may only qualify as having a protein tolerance of less than 15 g per day. In this context it may be reasonable for the cost-effectiveness of pegvaliase in the proposed population to serve as a proxy of that in the additional cohort." The evaluation considered that this was not reasonable. While the PBAC previously acknowledged that limited exploratory subgroup analyses suggested that sapropterin-responder status was not a treatment effect modifier (paragraph 7.4, pegvaliase PSD, July 2022 PBAC meeting), patients who respond to sapropterin, despite the low protein tolerance, should have better health outcomes (i.e. Phe-levels, liver outcomes and survival) than patients who do not respond, and potentially better utility. As such, the incremental benefit of pegvaliase compared to patients who did not respond to sapropterin was likely to be greater than when compared to patients who responded to sapropterin but have a protein tolerance less than 15 g/day.

6.49 Unchanged from the previous submission, a microsimulation approach was 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. Previously, "(t)he ESC considered that there was a lack

of clinical data available to support the microsimulation approach undertaken. While the resubmission 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" (paragraph 6.61, pegvaliase PSD, July 2022 PBAC meeting). While 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 ESC considered this justification was inadequate (paragraph 6.62, pegvaliase PSD, July 2022 PBAC meeting).

6.50 The resubmission noted that the clinical evidence and other input parameters that inform the economic analysis remained largely unchanged from the previous submission. The PBAC previously noted the following points that remain applicable to the model in the resubmission:

- Pegvaliase patients who respond in the model can respond either by achieving a blood-Phe < 360 µmol/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 two years in the model then switch to a Phe-restricted diet (paragraph 6.63, pegvaliase PSD, July 2022 PBAC meeting). The resubmission reiterated that the pegvaliase response rates are based on patients who received at least two years of treatment and therefore excluded patients who discontinued treatment as well as those with a treatment duration of less than two years. However, this likely resulted in the response rate being overestimated as patients experiencing a lack of clinical benefit or intolerance would be less likely to continue with treatment.
- Pegvaliase patients are assumed to experience a decrease in blood-Phe each cycle they remain on treatment until they reach a plateau of 261 µmol/L, unless they discontinue treatment and transition to a Phe-restricted diet. Patients treated with a Phe-restricted diet alone were assigned a once off improvement in blood-Phe of 108 µmol/L at the first cycle (paragraph 6.64, pegvaliase PSD, July 2022 PBAC meeting).
- For the model in the previous submission, 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 (paragraph 6.69, pegvaliase PSD, July 2022 PBAC meeting). The resubmission stated that the analysis

attempts to reflect the patient experience where small continuous changes in utility are accumulated to become clinically meaningful over time.

- In the pegvaliase arm of the model, the equations for estimating blood-Phe levels each cycle were based on the same data 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. Overall, the ESC considered there was limited testing for goodness of fit and a large amount of variance in the underpinning data (paragraph 6.65, pegvaliase PSD, July 2022 PBAC meeting). The resubmission stated that "During the evaluation of the previous submission, the Commentary, ESC and the PBAC highlighted several uncertainties with the additional analyses of PRISM and PKUDOS (e.g., blood Phe regression equations, goodness of fit statistics, etc). While acknowledged, no further analyses are available that allow for these issues to be addressed in this resubmission".
- The model assumed that Phe-restricted diet patients were unable to achieve a response, which contradicts the clinical evidence presented in the indirect naïve comparison The resubmission stated that due to the microsimulation approach (i.e. based on the measures of central tendency and spread of blood Phe at baseline), a small proportion of patients (< 1%) can be expected to achieve a blood Phe response. However, this was a much smaller proportion than was observed to respond based on data from PKUDOS i.e., 12% at six months.
- The utility values were based on a sponsor commissioned utility study which included a time trade off (TTO) (n=1,106) and discrete choice experiment (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) were correlated to blood-Phe categories assumed by the submission to correspond to the given health states (paragraph 6.68, pegvaliase PSD, July 2022 PBAC meeting). Based on previous submissions to the PBAC for sapropterin it was observed that the utility of uncontrolled PKU was underestimated, which favours pegvaliase (paragraph 6.70, pegvaliase PSD, July 2022 PBAC meeting).

6.51 For the previous pegvaliase submission, 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 (paragraph 7.11, pegvaliase PSD, 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). Despite this, the resubmission reduced the dose of pegvaliase (refer to paragraph 6.54).

6.52 The most notable change to the model since the previous submission was the pegvaliase cost per syringe (base case $[redacted] in the July 2022 submission compared with $[redacted] in the resubmission). As discussed in paragraph 3.2, the pegvaliase cost included the [redacted] the RSA [redacted]

6.53 In the model, the implementation of the incidence of pegvaliase AEs was revised to consider only the incidence of patients who experienced an AE of grade ≥ 3 which was applied in cycle one only. This has been modified since the previous submission where a probability was applied for each cycle for as long as the patient remained on treatment. The resubmission claimed that since the risk of events declines as treatment duration increases, the approach used in the previous submission overestimated the number of AEs of grade ≥ 3 experienced by patients treated with pegvaliase. Previously, 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 (paragraph 7.10, pegvaliase PSD, July 2-022 PBAC meeting). This issue remained in the current model and AE rates continued to be underestimated. Overall, the model was not particularly sensitive to the change made to AEs, reducing the ICER by [redacted]%. The pegvaliase AEs were not associated with a disutility, which may not be reasonable given the resubmission's clinical claim proposed that pegvaliase has inferior safety outcomes compared with a Phe-restricted diet.

6.54 While the previous submission assumed a pegvaliase mean dose of 30.5 mg/day based on data from PRISM 1 and 2, the resubmission's model assumed a mean dose of 24.5 mg based on the sponsor's database associated with the REMS program for patients who had been treated for at least 36 months. The resubmission claimed that the mean dose stabilises at around 24.5 mg/day after a follow-up time of least 36 months. It may not have been appropriate to use the mean dose for patients who had received three years of pegvaliase treatment. These data included treatment days in the

titration period, which is likely to underestimate the long-term average dose, particularly given the long titration period for pegvaliase (Lah 2022 reported that the mean time to maximum dose was 31.8 weeks). As observed above, the PBAC previously noted that the pegvaliase dose (30.5 mg) was underestimated compared with clinical practice (paragraph 7.11, pegvaliase PSD, July 2022 PBAC meeting). Consequently, the mean dose used in the resubmission is likely to be further underestimated. However, sensitivity analyses found the model was not particularly sensitive to this change (- 2.7%). Because the resubmission proposed the same price per syringe regardless of dose, the model was sensitive to the number of syringes per patient per day rather than the average dose per patient (refer to paragraph 6.74).

6.55 Table 11 provides a summary of the key drivers of the model. The economic model was most sensitive to the pegvaliase cost, the maintenance dose of pegvaliase and the utility values used in the model.

Table 11: Key drivers of the model

Description	Method/Value	Impact Base case $[redacted][1]/QALY
Pegvaliase price	While the model presented in the resubmission used a cost of $[redacted]	High. [redacted] then the price would be $510 and the ICER would increase to $[redacted]/QALY (+[redacted]%).
Number of pegvaliase syringes per day	The maintenance dose was assumed to be 24.5 mg/day based on sponsor data from the REMS program for patients who have a follow-up time of at least 36 months. However, as these data included the titration period, the long-term average dose was likely underestimated. However, the mean dose was similar with longer follow-up periods, which may reduce the risk that the method underestimates doses extrapolated over a longer treatment period (paragraph 6.74), albeit the 100 year time horizon applied in the economic model increases this uncertainty.	High. Assuming a maintenance dose of 60 mg/day increased the ICER to $[redacted][2]/QALY, an increase of [redacted]%.
Utility assumption	Based on mapping from TTO, the resubmission used a higher utility for the best responder health state (120-360 µmol/L, 0.775) 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 (>1,200 µmol/L, 0.37) categories increased the ICER to $[redacted][3], a [redacted]% increase.

Source: Constructed during the evaluation.
ICER = incremental cost effectiveness ratio; Phe = phenylalanine; QALY = quality adjusted life year gained; REMS = Risk Evaluation and Mitigation Strategy
The redacted values correspond to the following ranges:
[1] *$255,000 to < $355,0002*
[2] *$455,000 to < $555,000*
[3] *$355,000 to < $455,000*

6.56 The results of the stepped evaluation in the resubmission which are based on the means for the incremental cost and outcomes from 5,000 iterations are provided in Table 12.

Table 12: Results of the stepped economic evaluation (pegvaliase price = $[redacted])

Data	Costs			Outcomes			ICER
	Pegvaliase	Phe restricted diet alone	Incr	Pegvaliase	Phe restricted diet alone	Incr	
Step 1: Response rate with time horizon of 2 years	$[redacted]	$21,602	$[redacted]	90.30%	0.12%	90.18%	$[redacted][1] per responder
Step 2: Step 1 + extrapolation, background mortality, treatment discontinuation, transformation to QALYs	$[redacted]	$210,226	$[redacted]	12.22	8.76	3.46	$[redacted][2] per QALY
Step 3: Step 2 + continuing treatment criteria	$[redacted]	$210,226	$[redacted]	12.02	8.76	3.25	$[redacted][2] per QALY
Step 4: Step 3 + all resource use	$[redacted]	$240,710	$[redacted]	12.02	8.76	3.25	**$[redacted][2] per QALY**

Source: Table 3.8-2, p260 of the resubmission
ICER = incremental cost effectiveness ratio; Incr = incremental; Peg = pegvaliase; Phe = phenylalanine; QALY = quality adjusted life year gained
The redacted values correspond to the following ranges:
[1] *$155,000 to < $255,000*
[2] *$255,000 to < $355,000*

6.57 In the stepped economic evaluation, Step 1 included response rate with a time horizon of two years (to correspond to the timepoint at which patients are assessed for continued treatment with pegvaliase). Step 2, where response was transformed to QALYs and extrapolation, treatment discontinuations and background mortality were incorporated, represents the biggest impact on both costs and QALYs incurred in the model. Whereas Step 3 (including the continuing treatment criteria) and Step 4 (including all other resource-use) had only minor impacts on the ICER.

6.58 Table 13 provides an overview of the results of the economic evaluation for the resubmission's base case as well as alternative scenarios whereby the cost of pegvaliase is varied.

Table 13: Results of economic evaluation for different pegvaliase costs per syringe

	Pegvaliase	Phe-restricted diet	Incremental
Outcomes			
LYs	19.02	19.02	0
QALYs	12.02	8.76	3.25
ICERs			
Resubmission's base case: [redacted] as assumed in resubmission (pegvaliase cost = $[redacted])			
Total costs	$[redacted]	$240,710	$[redacted]
ICER/QALY			**$[redacted][1]**
Scenario: [redacted] as calculated based on PBAC inputs for 2022 submission (pegvaliase cost = $[redacted][a])			
Total costs	$[redacted]	$240,710	$[redacted]
ICER/QALY			**$[redacted][2]**
Scenario: [redacted] achieved (pegvaliase cost = $510.00[b])			
Total costs	$[redacted]	$240,710	$[redacted]
ICER/QALY			**$[redacted]**
Previous submission ICER/QALY (pegvaliase AEMP = $[redacted])			$[redacted][3]

Note: Results based on model run with 5000 iterations. Italicised data calculated during the evaluation.
Source: Table 3.8-2, p260 of the resubmission. Additional data compiled during the evaluation using Palynziq (pegvaliase) – CEA.xls
AEMP = Approved Ex-Manufacturer Price; DPMQ = dispensed price for the maximum quantity; ICER = incremental cost-effectiveness ratio; LY(G) = life year (gained); NA = not applicable; Phe = phenylalanine; QALY = quality-adjusted life year; RSA = risk sharing arrangement
[a] AEMP calculated based on the [redacted] where the proportion of patients followed-up at a metabolic clinic is 55% and the uptake rate is assumed to be [redacted]%).
[b] In the scenario where [redacted] the pegvaliase AEMP was assumed to equal the proposed DPMQ.
The redacted values correspond to the following ranges:
[1] $255,000 to < $355,000
[2] $355,000 to < $455,000
[3] $655,000 to < $755,000

6.59 The resubmission stated that the ICER was $255,000 to < $355,000 per QALY, based on a cost of $[redacted] per syringe. The ESC noted this was [redacted]% lower than the requested price (an ex-manufacturer price of $510 per syringe) on the basis that [redacted]. However, the ESC considered the model should have been based on a price of $510 per syringe, resulting in an ICER of [redacted] per QALY gained. The evaluation noted that a scenario based on an AEMP using inputs recommended by the PBAC ($[redacted]) resulted in an ICER of $355,000 to < $455,000 per QALY. The ESC considered this was an informative sensitivity analysis.

6.60 As observed for the 2022 pegvaliase model, the results in the resubmission were not technically the microsimulation results but were the ICER generated using the mean of the incremental QALY and incremental cost across all iterations, as opposed to probabilistically generating an ICER. During the evaluation the model was modified to produce the microsimulation results. Figure 4 shows the ICER scatterplot of the model base case over 5000 iterations, with each data point representing the incremental cost and incremental QALY reported for one iteration (i.e. one patient). It shows that for the majority of patients, the incremental cost was above $955,000 to < $1,055,000 as proposed in the resubmission's 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 line set to represent the resubmission's base case ICER of $255,000 to < $355,000/QALY. The cluster of data points near the origin (0,0) indicated the proportion of non-responders in the model.

Figure 4: Scatter plot of incremental cost vs incremental QALY over 5,000 iterations

Each data point represents the incremental cost and incremental QALY reported for one iteration (i.e. one patient).
Source: constructed during evaluation.

6.61 It was also noted that, as for the 2022 model, a number of the QALY results were negative – that is, patients treated with pegvaliase correlated with having worse outcomes. By relying on the mean of the incremental QALY it was assumed that QALYs gained by other patients would adequately compensate for disutilities experienced by some other patients, which may not be appropriate. As such, it may not be appropriate to use the mean of the incremental QALY in the estimation of the overall ICER without further justification.

6.62 The resubmission claimed that, for sapropterin, "despite the limitations of the cohort simulation model, the PBAC was sufficiently confident that the ICER based on this economic model would be in an acceptable range after reducing the proposed price by 50% to support a positive recommendation (paragraph 7.12, sapropterin PSD, July 2022 PBAC meeting). For this reason, the cohort simulation model as well as the approach to modelling changes in blood Phe over time and the associated QoL and cost impacts remain unchanged in this resubmission." The evaluation noted that while the PBAC recommended sapropterin for use in adults with HPA due to PKU, this economic model was not specifically approved or recommended by the PBAC in July 2022. Overall, in July 2022 the PBAC considered there were substantial limitations with the model and that it was not reasonable for the cost per patient to be the same in an initiating adult patient as in the existing listing of sapropterin which included paediatric and maternal patients. In July 2022, the PBAC considered the ICER was very high at the price proposed by the sponsor and considered that a substantial price reduction would be required to achieve a cost-effective listing for adult patients. In this context, the PBAC considered that in patients commencing treatment as an adult,

a 50% reduction in the price of sapropterin would be required. In July 2022, the PBAC noted this would reduce the ICER to $255,000 to < $355,000/QALY using the model provided with the sapropterin submission. In July 2022, the PBAC considered that with this reduction in price, the ICER, though very high and uncertain, would be acceptable in the context of the high clinical need, high burden of disease and small patient population where equity of access is an additional consideration (paragraph 7.12, sapropterin PSD, July 2022 PBAC meeting).

6.63 The results of key univariate sensitivity analyses are summarised in Table 14. As previously noted, the use of a microsimulation model resulted in unnecessarily complicated model, which required significant time to compute" (paragraph 6.61, pegvaliase PSD, July 2022 PBAC meeting). For this reason, during the evaluation the majority of sensitivity analyses were conducted using only 100 iterations.

Table 14: Sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER	% change to ICER
Sensitivity analyses presented in the resubmission (5000 iterations)[a]				
Base case	$	3.25	$ [1]	-
MBS benefit only	$	3.25	$ [1]	- %
Treat to max. pegvaliase dose (60 mg/day) (base case 24.5mg/day)	$	3.25	$ [2]	+ %
Discontinuations – old protocol	$	2.83	$ [1]	+ %
Discontinuations – new protocol	$	3.74	$ [1]	- %
Discount rate: 0% (base case 5%)	$	9.61	$ [1]	- %
Discount rate: 3.5% (base case 5%)	$	4.20	$ [1]	- %
Time horizon 30 years (base case 100)	$	2.69	$ [1]	+ %
Time horizon 40 years (base case 100)	$	2.99	$ [1]	+ %
Sensitivity analyses conducted during the evaluation (5000 iterations)				
Pegvaliase cost $ (base case $)	$	3.25	$ [3]	+ %
Pegvaliase cost $ (base case $)	$	3.25	$ [4]	- %
Pegvaliase cost $510.00 (base case $)	$	3.25	$	+ %
Sensitivity analyses conducted during the evaluation (100 iterations)				
Base case (100 iterations)	$	3.09	$ [1]	-
Time to pegvaliase response = 18 months (base case 24 months)	$	3.09	$ [1]	- %
Time horizon = 5 years (base case 100)	$	0.69	$ [1]	+ %
Time horizon = 10 years (base case 100)	$	1.30	$ [1]	+ %
Blood-Phe response rate = 51.7% for pegvaliase (base case 81.8%)[b]	$	1.99	$ [1]	+ %
Pegvaliase responder minimum blood Phe = 360 µmol/L (base case 261 µmol/L)	$	2.65	$ [3]	+ %
Use utilities from March 2018 submission - 0.71 for responder and 0.37 for uncontrolled (0.775 and 0.321 in base case, respectively)[c]	$	2.25	$ [3]	+ %
AEs incorporated as in 2022 model[d]	$	3.22	$ [1]	- %
Treat to max. pegvaliase dose (40 mg/day)	$	3.09	$ [1]	%
Pegvaliase mean dose 30.5 mg/day used in 2022 model (base case 24.5mg/day)[e]	$	3.22	$ [1]	- %
Patient body weight = 60.1 kg used in 2022 model (base case males 86.9 kg, females 72.9 kg)	$	3.09	$ [1]	+ %

Source: Table 3.8-2, p260 of the resubmission. Additional data compiled during the evaluation using Palynziq (pegvaliase) – CEA.xls
AEMP = Approved Ex-Manufacturer Price; ICER = incremental cost-effectiveness ratio; Phe = phenylalanine; QALY = quality-adjusted life year

[a] The sensitivity analyses presented in the resubmission were verified during the evaluation using 100 iterations. Consequently, the exact figures were not independently verified.

[b] Responders calculated using all patients used as the denominator (51.7% = 135/261), instead of the number of patients at risk.

[c] In sensitivity analyses, 0.71 utility for responder applied for blood Phe 120-360 µmol/L, and 0.37 utility for uncontrolled applied for blood Phe >1,200 µmol/L.

[d] Rows AD to AG of Sheet 'Trace – Int', Palynziq (pegvaliase) – CEA.xls modified to be the same as the respective rows in the model from the 2022 pegvaliase submission.

[e] F42:I48 of Sheet 'Resource Use - Meds, Palynziq (pegvaliase) – CEA.xls modified to be the same as the respective rows in the model from the 2022 pegvaliase submission.

The redacted values correspond to the following ranges:

[1] *$255,000 to < $355,000*

[2] *$455,000 to < $555,000*

[3] *$355,000 to < $455,000*

[4] *$155,000 to < $255,000*

6.64 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 to 51.7% (decreased from 81.8%,) only increased the ICER by [redacted]%. Given that the proportion of patients who achieve a blood-Phe ≤ 360 µmol/L was the key efficacy outcome upon which a clinical claim of superiority was made, the evaluation considered this result may reflect the inappropriateness of the assumptions underpinning the economic model.

Drug cost/patient/year

Table 15: Drug cost (maintenance dose) per patient for pegvaliase

	Trial dose and duration	Model	Financial estimates
Mean dose	31.8 mg/day[a]	24.5 mg/day[b]	
Mean duration	151.4 weeks (2.9 years) [a]	NR	NR
Cost/patient/month (cost = $[redacted] per syringe [redacted])[c]	$[redacted]	$[redacted]	
Cost/patient/year (cost = $[redacted] per syringe [redacted])[c]	$[redacted]	$[redacted]	
Cost/patient/year (cost = $[redacted] per syringe [redacted]	$[redacted]	$[redacted]	

Source: Table 2.4-5, p 94of the resubmission
NC = not calculable; NR = not reported

[a] The mean dose and mean duration for all of PRISM 2 were reported. In the trial, patients were restricted to either 20 mg or 40 mg of pegvaliase for PRISM Parts 1 to 3, and therefore the mean dose for PRISM 2 may not be representative of pegvaliase treatment outside of this trial.

[b] The resubmission derived the maintenance dose from the distribution of doses from the sponsor database associated with the pegvaliase REMS program, based on the mean daily dose at ≥ 36 months of follow-up. The mean dose of 24.5 mg/day was notably lower than assumed in the previous resubmission (30.5 mg/day), which was based on the weighted dose of the number of treatment days at each dosage, including titration period over five years for PRISM 1 and PRISM 2.

[c] Costs calculated based on a cost of $[redacted] per syringe. As the PI states that each syringe of pegvaliase is for single use only and any residue should be discarded, it was assumed that a dose of 31.8 mg was comprised of 2 x 20 mg/day and a dose of 24.5 mg was comprised of 1 x 20 mg + 1 x 10 mg. As the different strengths were priced the same, the daily cost was the same for 31.8 mg or 24.5 mg.

6.65 The cost of pegvaliase per patient per year calculated in the resubmission was $[redacted] based on a cost of $[redacted] per syringe. However, as previously noted, [redacted]

6.66 In the 2022 pegvaliase submission, for the model and financial estimates the cost/patient/year was $[redacted] (cost/patient/week = $[redacted]). This was considerably more than the current resubmission primarily due to the difference in assumed pegvaliase cost per syringe.

Estimated PBS usage & financial implications

6.67 This resubmission was not considered by DUSC, however DUSC did consider the July 2022 pegvaliase submission.

6.68 The key financial inputs for the financial estimates are presented in Table 16.

Table 16: Key inputs for financial estimates

Parameter	Value applied	Source/ Comment
Prevalence of HPA	1 per 11,226	Boneh 2006. The submission applied an age eligibility of age 16 and above to derive the eligible population. This was consistent with the 2022 submission.
PKU % of HPA	98.8%	Abadie 2001. This was consistent with the 2022 submission.
Patients (%) under routine follow-up for PKU	70.0%	Sponsor assumption. This was consistent with the 2022 submission; however as in the 2022 submission there was no justification provided for this assumption and the PBAC previously considered it may be an overestimate (paragraph 7.13, pegvaliase PDS, July 2022).
Patients (%) with blood Phe levels > 600 µmol/L	49.92%	Based on 21 studies included in the resubmission's literature search, where the average proportion of patients with blood Phe levels > 600 µmol/L was 49.92% (range: 28% - 100%; median: 75%). This was consistent with the 2022 submission.
Patients (%) achieving response to sapropterin	76.52% (1 minus 23.48% non-responders)	Additional analyses of PKUDOS based on response rate at 28 days. This was consistent with the 2022 submission.
Uptake rates	2026: [redacted]% 2027: [redacted]% 2028: [redacted]% 2029: [redacted]% 2030: [redacted]% 2031: [redacted]%	Assumption. This was consistent with the 2022 submission, however the PBAC previously considered these uptake rates were uncertain and may have been overestimated and questioned whether uptake rates would continue to increase over time (paragraph 7.13, pegvaliase PSD, July 2022).
Duration of treatment and persistence	Patients (%) with full year of treatment Year 1: 84.99% Year 2: 71.01% Year 3: 59.26% Year 4: 57.84% Year 5: 57.81% Year 6: 57.78%	Proportion of patients that remain on treatment in each year was derived from the economic model. These figures were similar but not identical to those in the 2022 submission. These values appear to visually align with the pegvaliase Markov trace in Figure 3.7-1 (p256) of the submission.
Distribution of pegvaliase strengths	Induction and titration: Based on TGA PI Maintenance dosing: 2.5 mg: 11.72% 10 mg: 96.89% 20 mg: 45.88% 40 mg: 11.87% 60 mg: 0.51%	The distribution of pegvaliase doses was based on data from the sponsor's database associated with the pegvaliase REMS program for patients with at least 36 months of follow-up and resulted in a mean dose of 24.5 mg/day. In the July 2022 submission, the distribution of doses was based on data from PRISM that reported a mean dose of 30.5 mg. In July 2022, the PBAC considered this mean dose (30.5 mg) was underestimated due to the use of study data that included a titration period, which was extrapolated over a longer period of time (paragraph 7.11, pegvaliase PSD, July 2022 PBAC meeting). Refer to paragraph 6.74.

Source: Table 4.1-1, pp266-268-313 of the resubmission.
ABS = Australian Bureau of Statistics; AEMP = Approved Ex-Manufacturer Price; DPMQ = dispensed price for the maximum quantity; HPA = hyperphenylalaninemia; Phe = phenylalanine; PI = product information; PKU = phenylketonuria; PSD = public summary document; REMS = Risk Evaluation and Mitigation Strategy

6.69 Table 17 presents the estimated use and financial implications for pegvaliase.

Table 17: Estimated use and financial implications (total pegvaliase DPMQ minus copayments)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed	[redacted][2]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][2]
Estimated financial implications of pegvaliase (published EMP = $510)[a]						
Cost to R/PBS	$[redacted][3]	$[redacted][4]	$[redacted][4]	$[redacted][5]	$[redacted][5]	$[redacted][6]
Cost of copayments	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]
Cost to PBS less copayments	**$[redacted][3]**	**$[redacted][4]**	**$[redacted][4]**	**$[redacted][5]**	**$[redacted][5]**	**$[redacted][6]**
Rebate (RSA)	$[redacted][8]	$[redacted][9]	$[redacted][9]	$[redacted][3]	$[redacted][3]	$[redacted][4]
Net cost R/PBS (proposed cap)	**$[redacted][10]**	**$[redacted][10]**	**$[redacted][10]**	**$[redacted][10]**	**$[redacted][11]**	**$[redacted][11]**
Estimated financial implications of pegvaliase (assumed effective cost = $[redacted])[b]						
Cost to R/PBS	$[redacted][10]	$[redacted][10]	$[redacted][10]	$[redacted][10]	$[redacted][11]	$[redacted][11]
Cost of copayments	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]
Cost to R/PBS less copayments (**proposed cap**)[c]	$[redacted][10]	$[redacted][10]	$[redacted][10]	$[redacted][10]	$[redacted][11]	$[redacted][11]
Net cost of affected medicine	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]
Net PBS cost (effective)	$[redacted][10]	$[redacted][10]	$[redacted][10]	$[redacted][10]	$[redacted][10]	$[redacted][11]
Net cost to MBS	$[redacted][12]	$[redacted][12]	$[redacted][12]	$[redacted][12]	$[redacted][12]	$[redacted][12]
Net cost to Government	**$[redacted][10]**	**$[redacted][10]**	**$[redacted][10]**	**$[redacted][10]**	**$[redacted][11]**	**$[redacted][11]**

Source: Tables 4.2-2, 4.2-3, 4.2-4, 4.2-5, 4.2-6, 4.2-7, 4.5-3, pp281-283 and 286 of the resubmission; paragraph 6.89, pegvaliase, PBAC Public Summary Document [PSD], July 2022 PBAC meeting

EMP = Ex-manufacturer price; RSA = Risk Sharing Arrangement

[a] The proposed annual caps for pegvaliase [redacted] published AEMP of $510 and an assumed effective cost of $[redacted].

[b] Under the proposed RSA, [redacted] $[redacted] per syringe [redacted]

[c] Calculations provided to demonstrate that the estimated financial implications using an assumed pegvaliase cost of $[redacted]

The redacted values correspond to the following ranges:

[1] 50 to < 500
[2] 5,000 to 10,000
[3] $60,000 to < $70,000
[4] $70,000 to < $80,000
[5] $80,000 to < $90,000
[6] $90,000 to < $100,000
[7] net cost saving
[8] $40 million to < $50 million
[9] $50 million to < $60 million
[10] $10 million to < $20 million
[11] $20 million to < $30 million
[12] $0 to < $10 million

6.70 The resubmission estimated that the total cost to the PBS of listing pegvaliase, [redacted] would be $60 million to < $70 million in Year 1, increasing to $90 million to < $100 million in Year 6.

6.71 The resubmission proposed Commonwealth expenditure caps of [redacted] in Year 1 increasing to [redacted] in Year 6, with a total of [redacted] in the first 6 years of listing. The resubmission proposed expenditure caps that [redacted] with an estimated total rebate to the Commonwealth of [redacted] in Year 1 increasing to [redacted] in Year 6.

6.72 Under the proposed RSA, the [redacted].

6.73 The eligible population was calculated using the same methodology as used in the previous submission. The evaluation and the ESC considered that two of the key issues raised by the PBAC in July 2022 had not been addressed:

- for the previous submission, the PBAC considered that the proportion of the adult PKU population who are under routine follow-up at metabolic clinics was likely overestimated and noted that for sapropterin it had considered that this proportion should be reduced from 70% to 55%. The PSCR justified maintaining this input at 70% by stating that the proportion has likely increased since the PBS-listing of sapropterin for adult patients. The ESC noted that no evidence was presented to justify this statement.
- for the previous submission, 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 (paragraph 7.13, pegvaliase PSD, July 2022 PBAC meeting).

6.74 The resubmission estimated a mean dose of 24.5 mg per day in the maintenance phase, based on data from patients with at least 36 months of follow-up. Limited information was provided about the analysis and it was unclear whether the reported average dose included the titration period. However, the mean dose was similar with longer follow-up periods (i.e. patients with follow-up of at least 48, 60 and 72 months reported mean doses of 25.1 mg, 24.5 mg and 23.6 mg per day, respectively), which may reduce the risk that the method underestimates doses extrapolated over a longer treatment period. The ESC noted that the dose distribution from the previous submission would result in a lower net PBS cost despite the higher mean dose (refer to Table 18). This appeared to be because different strengths were priced the same and thus the estimates were sensitive to the number of syringes per patient per day (rather than the mean dose). Further, there were differences in the methodology with the resubmission's revised source not appearing to include any patients on a dose of 0 mg, while the previous submission assumed that 12% of doses were 0 mg (the previous submission's approach may not have been appropriate given the financial estimates also included continuation assumptions).

6.75 A new issue to the resubmission was that the additional requested patient population of responders to sapropterin who have a protein tolerance < 15 g/day was not included in the resubmission's financial estimates. The resubmission claimed that "…clinicians have advised that most of these patients are likely to suffer from classical PKU and unlikely to achieve a response to sapropterin. Most of the small number of patients with a protein tolerance of less than 15 g per day are therefore likely already captured and any uncertainty around the size of this population is mitigated through the proposed risk sharing arrangement (RSA)".

6.76 The PBAC considered that the inclusion of the new patient group was unlikely to impact the financial estimates (refer to paragraph 6.4) and thus agreed with the resubmission's assumption that inclusion of this group would not increase the patient numbers.

6.77 The resubmission presented sensitivity analyses based on total cost of listing pegvaliase. These sensitivity analyses are presented in Table 18 and were recalculated during the evaluation to only account for net costs to the PBS of listing pegvaliase and thus represent [redacted] cost of $[redacted] per syringe [redacted] the net cost of affected medicines (i.e., savings of up to around $0 to < $10 million a year for reduced use of Phe-free supplements and other medicines).

Table 18: Sensitivity analyses ([redacted] cost of $[redacted] per syringe [redacted])

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Base case (**Scenario A**)	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][2]
Patients under clinic follow up (base case: 70%)[a]						
55%	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]
Phe > 500 µmol/L (base case: 49.92%) [b]						
75%	$[redacted][2]	[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][3]
40%	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]
Cumulative uptake rate (base case: [redacted]% in year 1, increasing by [redacted]% annually%)[c]						
[redacted]%, increasing by [redacted]% per year	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]
[redacted]%, increasing by [redacted]% per year	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]
Dose [d] (base case: based on patients with follow-up of at least 36 months, which estimated an average of 1.9 syringes per patient per day in the maintenance phase)						
July 2022 submission (1.6 syringes per day)	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]
PBAC recommended inputs from July 2022 (base case: Patients under clinic follow 70% in Year 1, uptake [redacted]% in Year 1 increasing by [redacted]% annually)						
Patients under clinic follow up 55% and uptake [redacted]% Year 1 increasing by [redacted]%	$[redacted][4]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]
Scenario B: Patients under clinic follow up 55%; and uptake [redacted]% Year 1 increasing by [redacted]% to [redacted]% in Years 4 to 6	$[redacted]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]
Patients under clinic follow up 55% and uptake [redacted]% Year 1 increasing by [redacted]%	$[redacted][4]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]

Note: As the resubmission presented sensitivity analyses based on total costs of listing pegvaliase, all figures were re-calculated during the evaluation to present net cost to the PBS.

Source: Table 4.6-1, p288 of the resubmission; Palynziq (pegvaliase) – UCM.xsl

PKU = phenylketonuria; HPA = hyperphenylalaninaemia

[a] PBAC recommended input = 55% (paragraph 7.13, pegvaliase PSD, July 2022 PBAC meeting).

[b] DUSC considered these inputs to be highly uncertain (Table 2, pegvaliase DUSC advice for the July 2022 PBAC meeting)

[c] The PBAC considered these uptake rates were uncertain and may have been overestimated (paragraph 7.13, pegvaliase PSD, July 2022 PBAC meeting).

[d] Because the resubmission proposed the same price per syringe regardless of dose ("flat pricing"), the financial estimates are sensitive to the estimated number of syringes per patient per day rather than the average dose per patient. In July 2022, the financial estimates were based on an average dose of 30.5 mg per day in the maintenance phase, which was assumed to be dispensed as: 11.9% of patients receiving 0 syringes per day; 32.3% receiving 1 syringe per day; 38.3% receiving 2 syringes per day; and 17.5% receiving 3 syringes per day. This resulted in an average of 1.6 syringes per patient per day. The resubmission assumed: 31.2% of patients receive 1 syringe per day; 46.1% receive 2 syringes per day; and 22.7% receive 3 syringes per day. This was an average of 1.9 syringes per patient per day.

The redacted values correspond to the following ranges:

[1] *$10 million to < $20 million*

[2] *$20 million to < $30 million*

[3] *$30 million to < $40 million*

[4] *$0 million to < $100 million*

6.78 The ESC noted the revised scenario ("Scenario B") with: (a) the proportion of patients under clinic follow-up reduced to 55%; and (b) uptake reduced to [redacted]% in Year 1 then increasing by [redacted]% per year in Years 2 to 4 and plateauing at [redacted]% in Years 4 to 6. The impact of this scenario [redacted] and net cost to the PBS is outlined in Table 19.

Table 19: [redacted] parameters for the revised scenario using the inputs outlined by the PBAC in July 2022

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Scenario A: Resubmission base case						
Number of patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed	[redacted][2]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][2]	[redacted][2]
Cost to R/PBS (at published EMP = $510)	**$[redacted][4]**	**$[redacted][5]**	**$[redacted][5]**	**$[redacted][6]**	**$[redacted][6]**	**$[redacted][7]**
[redacted]	$[redacted][8]	$[redacted][9]	$[redacted][9]	$[redacted][4]	$[redacted][4]	$[redacted][5]
Net cost R/PBS (proposed cap)	**$[redacted][10]**	**$[redacted][3]**	**$[redacted][3]**	**$[redacted][3]**	**$[redacted][4]**	**$[redacted][4]**
Scenario B: using the inputs outlined by the PBAC in July 2022						
Number of patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Cost to R/PBS (at published EMP = $510)	**$[redacted][7]**	**$[redacted][8]**	**$[redacted][8]**	**$[redacted][8]**	**$[redacted][8]**	**$[redacted][8]**
[redacted]	$[redacted][9]	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]
Net cost R/PBS ([redacted] cost of $[redacted] per syringe)	**$[redacted][10]**	**$[redacted][10]**	**$[redacted][10]**	**$[redacted][10]**	**$[redacted][10]**	**$[redacted][10]**
Net cost of affected medicines	-$[redacted][11]	-$[redacted][9]	-$[redacted][9]	-$[redacted][9]	-$[redacted][9]	-$[redacted][9]
Net cost to R/PBS	**$[redacted][10]**	**$[redacted][3]**	**$[redacted][3]**	**$[redacted][3]**	**$[redacted][3]**	**$[redacted][3]**
[redacted]						**$[redacted]**
Scenario C: [redacted] as proposed by sponsor [A] but expenditure as per July 2022 PBAC inputs [B]						
Number of scripts dispensed [B]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Cost to R/PBS (at published EMP = $510) [B]	**$[redacted][8]**	**$[redacted][9]**	**$[redacted][9]**	**$[redacted][9]**	**$[redacted][9]**	**$[redacted][9]**
Net cost to R/PBS (cap proposed by sponsor) [A]	$[redacted][10]	$[redacted][10]	$[redacted][10]	$[redacted][10]	$[redacted][12]	$[redacted][12]
[redacted]	$[redacted][12]	$[redacted][13]	$[redacted][13]	$[redacted][13]	$[redacted][13]	$[redacted][13]
Net cost of affected medicines	-$[redacted][11]	-$[redacted][11]	-$[redacted][11]	-$[redacted][11]	-$[redacted][11]	-$[redacted][11]
Net cost to R/PBS	$[redacted][10]	$[redacted][10]	$[redacted][10]	$[redacted][10]	$[redacted][12]	$[redacted][12]
[redacted] cost per syringe	$[redacted] (ICER of $[redacted][10]/ QALY) $[redacted]					

Source: Prepared during preparation of the ESC Advice
RSA = Risk Sharing Arrangement
The redacted values correspond to the following ranges:
[1] *50 to < 500*
[2] *5,000 to < 10,000*
[3] *500 to < 5,000*
[4] *$60 million to < $70 million*
[5] *$70 million to < $80 million*
[6] *$80 million to < $90 million*
[7] *$90 million to < $100 million*
[8] *$40 million to < $50 million*
[9] *$50 million to < $60 million*
[10] *$10 million to < $20 million*
[11] *net cost saving*
[12] *$20 million to < $30 million*
[13] *$30 million to < $40 million*

6.79 The ESC noted that in order to [redacted] cost of $[redacted] per syringe [redacted].

6.80 The PSCR stated that [redacted] If the expenditure thresholds ('caps') [redacted] ICER of $355,000 to < $455,000 per QALY as shown in Table 13.

Quality Use of Medicines

6.81 As in the previous submission, the resubmission did not provide any Quality Use of Medicines information.

Financial Management – Risk Sharing Arrangements

6.82 The resubmission proposed an RSA for pegvaliase. An RSA was not proposed in the previous pegvaliase submission.

6.83 The resubmission claimed that the sponsor [redacted] through an RSA [redacted] cost of $[redacted] per syringe (as calculated at an "ex-manufacturer" level, which corresponds to a "DPMQ level" of $[redacted] per syringe i.e., with mark-ups included). [redacted] proposed expenditure cap was $10 million to < $20 million in Year 1 increasing to $20 million to < $30 million in Year 6.

6.84 The resubmission and the PSCR stated that the proposed RSA [redacted] The PSCR stated [redacted]. The PSCR acknowledged the uptake rates were uncertain but maintained the reasonableness of other parameters (refer to paragraph 6.73). The pre-PBAC response also reiterated that [redacted]

6.85 The ESC considered that the [redacted] (i.e. the submission estimated PBS expenditure of $400 million to < $500 million over six years, [redacted] The ESC considered that the uncertain financial estimates and high financial impact means that the resubmission's RSA proposal may present a high level of risk to Government.

6.86 While the resubmission presented an [redacted] pegvaliase cost of $[redacted] per syringe, Figure 5 shows [redacted]

Figure 5: Pegvaliase cost per syringe under the proposed RSA

Source: Constructed during the evaluation using 'Palynziq (pegvaliase) – UCM'.
AEMP = approved ex-manufacturer price; RSA = Risk Sharing Arrangement

Using the resubmission's financial estimates workbook [redacted] in Year 1, the effective AEMP went above $510, which was presumed to be an error.

6.87 Inclusion of financial estimate inputs as recommended by the PBAC in July 2022 would result in a [redacted] If the proportion of patients followed up at a metabolic clinic is assumed to be 55% and the uptake rate is assumed to be [redacted]% (Year 1), [redacted]

7 PBAC Outcome

7.1 The PBAC deferred making a recommendation regarding pegvaliase for the treatment of patients with phenylketonuria (PKU) who have inadequate blood phenylalanine (Phe) control despite prior management with available treatment options including a Phe restricted diet and sapropterin. The PBAC was satisfied that pegvaliase provides, for some patients, a significant improvement in efficacy over a Phe-restricted diet alone. The PBAC reaffirmed its view that there is a high clinical need for effective treatments in this patient population, however the PBAC considered it was unclear whether the sponsor's pricing and risk sharing arrangement (RSA) proposal would achieve a cost-effective price and adequately manage the financial risk to the Commonwealth. The deferral was to allow further consultation with the sponsor and the Department regarding how best to implement the intent of the sponsor's requested pricing and RSA proposal.

7.2 The PBAC welcomed input from individuals and the Metabolic Dietary Disorders Association. The input described the challenges of living with PKU including the severe and lifelong burden of dietary restrictions. The input also outlined the cognitive impacts of high Phe levels including difficulty concentrating, reduced mental clarity, anxiety and fatigue. The input described current treatments as often

being inadequate at improving dietary restrictions. The comments outlined a hope that pegvaliase would be more effective than existing therapies, allowing less-strict dietary restrictions and improved cognitive function. Consumers acknowledged the adverse event profile of pegvaliase (i.e. possible anaphylaxis, immune responses and daily injections) but these were seen as manageable with the benefits outweighing the risks.

7.3 The PBAC considered this was supportive of the consumer input received for the July 2022 submissions for medicines to treat PKU (pegvaliase and sapropterin) which noted the specific challenges for adults living with PKU including 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. 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. The PBAC considered that the consumer input had identified and described outcomes that were not well-captured in the clinical or economic evidence for pegvaliase.

7.4 The PBAC considered that, based on the consumer input, there remains a high unmet need for effective treatments in the proposed patient population (i.e. patients who have inadequate Phe levels despite prior management with available treatment options).

7.5 Input was also received from five clinicians or groups specialising in metabolic conditions about specific issues relating to the place in therapy and restriction (refer to paragraph 6.4, and discussed in relevant paragraphs below).

Restriction

7.6 The restriction proposed in the resubmission required patients to demonstrate a response at any timepoint between 21 weeks (i.e., approximately 5 months) and 24 months. However, the PBAC recalled that the ESC previously considered that up to 24 months "was an inappropriately long period of time for patients to be on treatment without assessing whether the benefits were outweighing the risks" (paragraph 3.3, pegvaliase PSD, July 2022 PBAC meeting). The PBAC noted that the Product Information states 'The majority of patients (67%) reached a response by 18 months of total treatment. An additional 8% of patients responded after 18 months of treatment. If a patient does not reach a clinically relevant blood phenylalanine reduction after 18 months of treatment, continuation should be reconsidered. The physician may decide, with the patient, to continue pegvaliase treatment in those patients who show other beneficial effects (e.g., ability to increase protein intake from intact food or improvement of neurocognitive symptoms)'. The PBAC considered that it may be reasonable to assess response at 18 months, with patients

who have not reached target Phe levels being able to continue for a further 6 months (i.e., total duration of 24 months of therapy) only if they have experienced improvements in protein tolerance and/or neurocognitive function. This was supported by the clinician input (refer to paragraph 6.4) which generally agreed with the resubmission's proposed timeframe (i.e. up to 24 months), with one suggesting response assessment timepoints at 16-24 weeks, 52 weeks and 24 months for 'slow responders'.

7.7 The requested restriction defined response as at least one of either Phe blood level < 360 µmol/L or a ≥ 5-point improvement in the inattention subscale of the Attention Deficit Hyperactivity Disorder Rating Scale (ADHD-RS) score. The PBAC agreed with clinician input (refer to paragraph 6.4) that response should be based on Phe levels over a series of time (e.g. 4 samples in a one month period with < 360 µmol/L), and that ADHD-RS scores should not be part of the response assessment given these are not validated for this purpose. As noted in paragraph 7.6, the PBAC considered there may be a role for response assessment to be based on protein tolerance and/or neurocognitive function at 18 months.

7.8 The pegvaliase Product Information states 'patients should be instructed to carry an adrenaline injection device with them at all times during pegvaliase treatment.' However, the PBAC considered it remained unclear how patients would access adrenaline auto-injectors in practice given PBS supply must be initiated by, or in consultation with a clinical immunologist / allergist / paediatrician / respiratory physician (or patients discharged from hospital or an emergency department after treatment with adrenaline). The PSCR indicated that metabolic physicians could consult with relevant specialists, however the PBAC noted that some of the clinicians / groups specialising in metabolic conditions (who were consulted about specific issues) indicated this may not always be feasible (refer to paragraph 6.4).

7.9 With regard to other elements of the requested listing, the PBAC was of a mind that:

- the listing should be General schedule Authority required (telephone/online PBS authorities system).
- the restriction should be age agnostic.
- Nurse Practitioner and medical practitioner prescribing should be permitted in both the initiation and the continuation treatment phases but in consultation with a metabolic physician. The full treatment criteria should state: 'Must be treated by a metabolic physician or Must be treated by a health practitioner who is any of (i) a medical practitioner, (ii) a nurse practitioner, in consultation with a metabolic physician'. The PBAC considered that similar flow-on changes to the PBS listings for sapropterin and betaine may also be reasonable for consistency (given these are also medicines to treat rare inherited metabolic disorders).
- daily protein tolerance < 15 g per day could generally be quantified in practice.

- it would be reasonable for patients to switch back to sapropterin if they experience an inadequate response or intolerance to pegvaliase.
- the following maximum quantities and repeats would be appropriate:
    - 2.5 mg: initial (max qty 6 pre-filled syringes with 0 repeats) and continuing (max qty 84 pre-filled syringes with 5 repeats);
    - 10 mg: initial (max qty 14 pre-filled syringes with 0 repeats) and continuing (max qty 28 pre-filled syringes with 5 repeats); and
    - 20 mg: initial (max qty 90 pre-filled syringes with 5 repeats) and continuing (max qty 90 pre-filled syringes with 5 repeats).

Clinical place and comparator

7.10 The PBAC recalled that in July 2022 it had considered the proposed clinical place, as last-line after sapropterin, to be inequitable and not clinically appropriate as it was inconsistent with the clinical evidence and may exclude some patients who may benefit from pegvaliase e.g., patients who are responding sub-optimally to sapropterin (paragraph 7.4, pegvaliase PSD, July 2022 PBAC Meeting). The PBAC noted that, to address this, the resubmission included an additional group of patients with a protein tolerance of < 15g per day, but who have responded to sapropterin (i.e. met the PBS criteria of ≥ 30% reduction in blood Phe from baseline). The PBAC considered the inclusion of this new group was appropriate, noting it was supported by MDAA and the five clinicians/metabolic units.

7.11 While the PBAC considered it was not ideal to restrict pegvaliase to last line after sapropterin, the Committee considered it was acceptable in the context of the high clinical need in this group along with the adverse event profile of pegvaliase and the potentially long timeframe between initiation and response.

7.12 The PBAC considered that the nominated comparator, a Phe-restricted diet alone, was an appropriate comparator in the context of the proposed restriction. While sapropterin may be a potential comparator in the new group of patients who are 'responding' to sapropterin but with protein tolerance of < 15g per day, the PBAC considered this group was likely to comprise a small number of patients given most would have classical PKU and are unlikely to meet the PBS sapropterin response criteria (refer to paragraph 6.4).

Comparative effectiveness and clinical claim

7.13 For the July 2022 pegvaliase submission, the PBAC considered that while pegvaliase appeared 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 (paragraph 7.8, pegvaliase, PSD, July 2022 PBAC meeting). The PBAC noted that the resubmission had provided a new analysis (Burton 2024) but considered it did not further inform the magnitude of the incremental benefit as it was based on

the same underlying data as the previous analyses and had similar limitations (including the lack of common comparator arm and transitivity issues).

7.14 The PBAC considered the claim of inferior safety compared with a Phe-restricted diet alone was adequately supported by the data, particularly noting the higher rates of hypersensitivity and generalised skin reactions associated with pegvaliase.

Economic analysis

7.15 The PBAC noted that the resubmission used the same economic model structure with predominantly the same inputs as the July 2022 submission. The PBAC recalled the ESC's previous advice regarding the substantial limitations of the economic model, including that the model was highly uncertain and 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' (paragraph 7.11, pegvaliase PSD, July 2022 PBAC Meeting). However, the PBAC reiterated its previous considerations (for medicines to treat PKU) that clinically significant outcomes may not have been fully captured in the economic evaluation (refer to paragraph 7.3).

7.16 The PBAC noted the resubmission's base case ICER was $255,000 to < $355,000 per QALY, reduced from $655,000 to < $755,000/QALY in the previous submission. In July 2022 the PBAC considered that the ICER for pegvaliase should be 'no higher than that accepted for sapropterin for initiation in adult patients' (paragraph 7.12, pegvaliase PSD, July 2022 PBAC Meeting), which was $300,000/QALY (paragraph 7.12, sapropterin Public Summary Document [PSD], July 2022 PBAC Meeting). The PBAC considered that the ICER proposed in the resubmission, though very high and uncertain, would be acceptable in the context of the very high clinical need, high burden of disease and small patient population, and also reiterated that the clinical meaningfulness of the benefits in adults was not fully captured in the economic evaluation.

7.17 The PBAC noted that the ICER of $255,000 to < $355,000 per QALY was based on a pegvaliase cost of $[redacted] per syringe. This was [redacted]% lower than the requested price (an ex-manufacturer price of $510 per syringe) on the basis that [redacted]. As such, the submission's base case ICER [redacted] The PBAC noted that if pegvaliase utilisation is lower than estimated, [redacted] at the requested ex-manufacturer price of $510 per syringe, the ICER was estimated to be [redacted]. As such, the PBAC considered that a high degree of confidence would be required that the pricing, financial and RSA arrangements [redacted] the ICER of around $255,000 to < $355,000 /QALY).

Financial estimates

7.18 The PBAC noted the financial estimates were based on many of the same inputs as the July 2022 submission. The PBAC considered that the resubmission had not

adequately addressed the Committee's previous concerns that: the proportion of the adult PKU population who are under routine follow-up at metabolic clinics was likely overestimated; and the assumed uptake rates were uncertain and may have been overestimated (refer to paragraph 6.73).

7.19 In particular, the PBAC considered that the utilisation estimates in later years (Years 3 to 6) were less certain than the estimates in the first two years. In the first two years, the PBAC considered the uptake rates were unlikely to be overestimated as there may be pent-up demand and thus a reasonable level of initial uptake among the prevalent population in Years 1 and 2. In later years, the PBAC considered utilisation was more difficult to predict given the potential for changes to treatment algorithms and clinical practice over time.

7.20 Consequently, the PBAC considered that the utilisation estimates presented in the resubmission were uncertain and may have been overestimated particularly in later years, and thus the PBAC had low confidence that the utilisation levels required to achieve the intended rebates would be met.

Deferral

7.21 The PBAC considered that there was a low level of certainty that the sponsor's pricing [redacted] would achieve an acceptably cost-effective price and adequately manage the financial risk to the Commonwealth. The deferral was to allow further consultation with the sponsor and the Department regarding how best to implement the [redacted] achieving a cost-effective listing for pegvaliase.

Outcome:
Deferred

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 patients, healthcare professionals, and the MDDA for their valuable input to this submission and looks forward to engaging constructively with the PBAC and the Department to identify a path forward.