Cost-effectiveness of pegvaliase (Palynziq®) for the treatment of patients with phenylketonuria aged 16 years or over, who have inadequate blood phenylalanine control (blood phenylalanine levels over 600 micromol/L) despite prior management with available treatment options.

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of pegvaliase (Palynziq®) for patients with phenylketonuria aged 16 years or over, as per the product licence. Following assessment of the Applicant's submission, the NCPE recommends that pegvaliase (Palynziq®) be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013. The Health Service Executive (HSE) asked the NCPE to carry out a review of the Applicant's (Biomarin) Health Technology Assessment of pegvaliase (Palynziq®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective, including the clinical effectiveness and health-related quality of life benefits, which the new treatment may provide and whether the cost requested is justified. Following the recommendation from the NCPE, the HSE examines all the relevant evidence. The final decision on reimbursement is made by the HSE. In the case of cancer drugs, the National Cancer Control Programme (NCCP) Technology Review Group also considers the NCPE recommendation.

About the National Centre for Pharmacoeconomics

The NCPE are a multidisciplinary team including clinicians, pharmacists, pharmacologists, information specialists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area. Our aim is to provide impartial advice to help decision-makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **September 2022**

Summary

In October 2021, Biomarin resubmitted a dossier of clinical, safety and economic evidence on pegvaliase (Palynziq®) for the treatment of patients with phenylketonuria aged 16 years or over, who have inadequate blood phenylalanine control (blood phenylalanine levels over 600 micromol/L) despite prior management with available treatment options. Biomarin are seeking reimbursement for pegvaliase under the High Tech Drug Arrangement.

Phenylketonuria (PKU) is an inherited, autosomal recessive disease characterized by a deficiency in the intracellular liver enzyme phenylalanine hydroxylase (PAH). PAH deficiency results in an abnormally elevated concentration of phenylalanine, which is toxic to the brain.

Pegvaliase is a PEGylated recombinant phenylalanine ammonia lyase enzyme that converts phenylalanine to ammonia and trans-cinnamic acid that are primarily eliminated by liver metabolism. Pegvaliase is indicated for the treatment of patients with PKU aged 16 years or over who have inadequate blood Phenylalanine (Phe) control (defined as blood Phe levels greater than 600 micromol/L) despite prior management with available treatment options. Pegvaliase is available, as a solution for subcutaneous injection, in single-use, prefilled syringes. The recommended induction dose of pegvaliase is 2.5 mg once per week for four weeks. The dose should then be titrated gradually, based on tolerability, to a once-daily maintenance dose. The maintenance dose is individualised to achieve blood Phe control (i.e. a Phe level of 120 to 600 micromol/L), considering tolerability and dietary protein intake. Dietary Phe intake should remain consistent until a maintenance dose is established and thereafter. Due to the potential for an acute systemic hypersensitivity reaction, premedication prior to each dose is required during induction and titration. Initial administration(s) should be performed under supervision of a healthcare professional and patients should be closely observed for at least one hour following each of these initial injection(s). For at least the first six months of treatment when the patient is self-injecting (i.e. when administration is not under healthcare professional supervision), an observer must be present during and for at least one hour after each administration. After six months of pegvaliase treatment, the need for an observer may be reconsidered. Treatment is lifelong.

The current standard of care, in Ireland, for patients, aged over 16 years, with PKU is a Phe-restricted diet (hereafter referred to as 'diet'). Sapropterin (a synthetic form of tetrahydrobiopterina cofactor to PAH) is also available under a managed access programme for adult and paediatric patients 18 years or under with PKU who have been shown to be responsive to treatment. Sapropterin is taken in conjunction with a Phe-restricted diet. It is administered orally and dosed according to body weight.

The Applicant anticipates that pegvaliase will be used in accordance with the licensed indication and has also identified a subgroup, with consistently high blood Phe levels (over 1200 micromol/L) as having the greatest unmet need. Clinical opinion, provided by the Applicant, also considers that this subgroup would benefit the most from treatment with pegvaliase.

1. **Comparative effectiveness of pegvaliase**

The efficacy and safety of pegvaliase was studied in two phase III clinical trials (PRISM-1 and PRISM-2) in adult patients with PKU with blood Phe concentrations greater than 600 micromol/L on existing management. Most patients were on an unrestricted diet prior to and during the trials. PRISM-1 (n=261) was a randomised, open-label trial in patients treated with titrated doses of pegvaliase up to a maintenance dose of either 20 mg once daily or 40 mg once daily. About 75% (n=196) of patients had been previously treated with sapropterin and about 57% had been dependent on medical nutritional treatment as part of a Phe-restricted diet. Of those previously treated with sapropterin, 144 were non responders to saproterin and 52 were responders. Both maintenance doses resulted in a reduction in Phe concentration. The dose effect was not linear. PRISM-1 was the major feeder study for PRISM-2.

PRISM-2 was a randomised, double blind, placebo controlled, four arm, discontinuation study to evaluate the efficacy and safety of self-administered, pegvaliase in adults (n = 215). All patients had previously been treated with pegvaliase. Patients were required to have the neurocognitive and linguistic capacity to comprehend the Profile of Mood States (POMS) psychological Rateing Scale (RS). In addition, participants were required to have a competent person, aged over 18 years, who could observe them after injections for at least one hour. PRISM-2 was conducted in four parts. Part 2 provided key efficacy outcomes: the primary efficacy endpoint was change in blood Phe concentration. The secondary efficacy endpoints were mood and inattention

symptoms measured by changes in neurocognitive and neuropsychiatric symptom scores, changes in Attention Deficit Hyperactivity Disorder (ADHD)- RS (investigator rated), change in PKU specific POMS-RS (self rated). There was a statistically significant change in blood Phe concentration with 20 mg once daily [least squares mean (LSM) change -973.0 µmol/L (95%CI -1204.2, -741.9) p<0.0001] and 40 mg once daily [LSM change -588.5 µmol/L (95%CI -830.1, -346.9) p<0.0001]. There was no clinically significant change in neurocognitive and neuropsychiatric symptom scores; this was expected due to the short (8-week) duration of Part 2. In Part 4, long term efficacy was investigated through an open-label extension phase up to week 41. Reductions in blood Phe were observed and sustained in patients with available week 41 data (n=170). Patients who did not have a 20% reduction in blood Phe level from naïve baseline before entry into Part 4, were eligible to enter Part 4 and receive a 60 mg once daily dose. After 41 weeks of long term dosing in Part 4, patients in this group (n=57) had a mean reduction of 34.9% in blood Phe levels from naïve baseline. After 18 months of treatment, there was an improvement in inattention subscale score (as measured by ADHD RS-IV). These changes were of greater magnitude in those who were more symptomatic at baseline.

An indirect treatment comparison (ITC) was conducted to compare the efficacy of pegvaliase & diet vs sapropterin and diet and vs diet alone. A cohort of patients who received pegvaliase and diet in the phase II 165-205 trial (an open label dose finding study where pegvaliase was administered using the induction/titration/maintenance dosing regimen) or phase III PRISM studies were compared, using a propensity score matching approach, with a historical control, who had received sapropterin and diet or diet alone, from the PKU Demographics, Outcome, and Safety (PKUDOS) Registry. The outcomes evaluated included change in blood Phe concentration and natural protein intake after 1 and 2 years of treatment. Greater decreases in blood Phe levels and increases in protein intake from natural food were estimated for patients treated with pegvaliase- compared with patients receiving sapropterin and diet or diet alone. However, it is difficult to draw conclusions on the comparative effectiveness of pegvaliase vs sapropterin & diet, and diet alone due to the limitations of the ITC.

2. Safety of pegvaliase

The safety data for pegvaliase is taken from the induction/titration/maintenance population (n=285) which includes data from patients first enrolled in the parent studies 165-205 or PRISM-1 and from the subsequent extension studies to which they transferred. The most common adverse events (AEs), affecting over 50% of those treated with pegvaliase, included injection site reactions (93.3%), hypersensitivity (74.7%), arthralgia (84.6%) and headache (54.7%). High rates of hypersensitivity reactions and AEs were observed (n = 213 (74.7%)). Most acute hypersensitivity reactions occurred in the first year. There were 91 serious adverse events (SAE) in 64 of 285 patients in the induction, titration, and maintenance phases. The most common SAEs were anaphylaxis (14 patients) and hypersensitivity (9 patients). There were 18 SAEs that resulted in study drug or study discontinuation, most of these were related to hypersensitivity. Hypersensitivity reactions were mild in 18.2%, moderate in 62.5%. They were most frequent during the first six months of treatment. There were 16 patients who experienced 25 acute systemic hypersensitivity events.

3. Cost effectiveness of pegvaliase

A cost-utility analysis was performed using a six-state Markov model with a life-time horizon. Treatment with pegvaliase followed the induction/titration/maintenance dosing regimen and was informed from patients in the pegvaliase Phase 2 165-205 trial and the Phase 3 trials. The modelled population, in the Applicant's base case analysis, was in accordance with the licensed indication. A scenario analysis also considered the subgroup with blood Phe level consistently over 1200 micromol/L. The comparators included were diet alone and sapropterin and diet.

Treatment effectiveness was informed by the ITC. Health-state utility values were informed by a time trade off study conducted in Sweden, identified through a systematic literature review. The Review Group noted a number of key limitations with the analysis including the model structure and certain assumptions.

The Review Group made a number of changes to the Applicant's base case model. These included a stopping rule for both sapropterin (after year 1) and pegvaliase (after year 2); costing sapropterin as a hospital-reimbursed product; and incorporating variability in the maintenance dose of pegvaliase.

Results of the Applicant's base case, and the NCPE-adjusted base case, are illustrated in Tables 1 and 2, respectively.

Table 1(a): Results of the Applicant's base case analysis of pegvaliase vs diet alone

Treatment	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Diet	€104,947	5.12	–	–	–
Pegvaliase & diet	€717,161	7.58	€612,215	2.46	€248,790

ICER: incremental cost-effectiveness ratio; **QALY:** quality-adjusted life-year **Phe**, phenylalanine
ICERs presented are based on the list price of both drugs.
Note: Numbers are presented as rounded; calculations may not be directly replicable. A discount rate of 4% on costs and outcomes is applied.

Table 1(b): Results of the Applicant's base case analysis of pegvaliase vs sapropterin & diet

Treatment	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Sapropterin & diet	€2,662,042	3.54	–	–	–
Pegvaliase diet	€804,505	8.27	-€1,857,538	4.74	Dominant

ICER: incremental cost-effectiveness ratio; **QALY:** quality-adjusted life-year **Phe**, phenylalanine
ICERs presented are based on the list price of both drugs.
Note: Numbers are presented as rounded; calculations may not be directly replicable. A discount rate of 4% on costs and outcomes is applied.

Table 2(a): Results of the NCPE-adjusted base case analysis of pegvaliase vs diet alone

Treatment	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Diet	€104,947	5.12	–	–	–
Pegvaliase & diet	€843,353	7.21	€738,407	2.09	€354,132

ICER: incremental cost-effectiveness ratio; **QALY:** quality-adjusted life-year **Phe**, phenylalanine
ICERs presented are based on the list price of both drugs.
Note: Numbers are presented as rounded; calculations may not be directly replicable. A discount rate of 4% on costs and outcomes is applied.

Table 2(b): Results of the NCPE-adjusted base case analysis of pegvaliase vs sapropterin & diet

Treatment	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Sapropterin & diet	€929,826	5.04	–	–	–
Pegvaliase & diet	€989,623	7.65	€59,796	2.61	€22,209

ICER: incremental cost-effectiveness ratio; **QALY:** quality-adjusted life-year **Phe,** phenylalanine
ICERs presented are based on the list price of both drugs.
Note: Numbers are presented as rounded; calculations may not be directly replicable. A discount rate of 4% on costs and outcomes is applied.

Based on the NCPE-adjusted base case analysis, the probability of cost effectiveness of pegvaliase vs diet alone at the €45,000/QALY threshold was 0.82% and vs sapropterin and diet was 47%.

The Applicant also presented scenario analyses in the subgroup with blood Phe consistently greater than 1,200 micromol/L. Results, using the NCPE-adjusted base case, are presented in Table 3.

Table 3(a): Results of the NCPE analysis of pegvaliase vs diet alone in patients with blood Phe greater than 1,200 micromol/L

Treatment	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Diet	€104,962	4.53	–	–	–
Pegvaliase & diet	€786,949	6.82	€681,987	2.29	€298,321

ICER: incremental cost-effectiveness ratio; **QALY:** quality-adjusted life-year **Phe**, phenylalanine
ICERs presented are based on the list price of both drugs.
Note: Numbers are presented as rounded; calculations may not be directly replicable. A discount rate of 4% on costs and outcomes is applied

Table 3(b): Results of the NCPEanalysis of pegvaliase vs sapropterin and diet in patients with blood Phe greater than 1,200 micromol/L

Treatment	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Sapropterin & diet	€260,188	4.90	–	–	–
Pegvaliase & diet	€1,039,926	7.66	€779,737	2.77	€281,865

ICER: incremental cost-effectiveness ratio; **QALY:** quality-adjusted life-year **Phe**, phenylalanine
ICERs presented are based on the list price of both drugs.
Note: Numbers are presented as rounded; calculations may not be directly replicable. A discount rate of 4% on costs and outcomes is applied

Diet is the primary comparator. The NCPE conducted a price-ICER analysis for the comparison of pegvaliase vs diet alone in the licensed population. A reduction of about 87% in the price to wholesaler (PtW) for pegvaliase would be required in order for it to be deemed cost effective.

4. Budget impact of pegvaliase

The PtW of pegvaliase per one prefilled syringe (2.5mg, 10mg or 20mg) is €248.43. The total cost to the HSE (excluding VAT and High-Tech pharmacy fee) is €254.64. The total drug cost to the HSE for year 1 was estimated to be €105,886 (excl. VAT, incl. pharmacy fees) or €131,366 (incl VAT, incl. pharmacy fees). The total drug cost to the HSE for subsequent years was estimated at €121,654 (excl VAT) per annum or €150,956 (incl VAT) per annum.

Assuming number of patients treated are three (in year 1), six (in year 2), 11 (in year 3), 11 (in year 4) and 15 (in year 5), the 5-year cumulative gross drug budget impact is about €6.9m. The Applicant presented a world 'with' and 'without' pegvaliase. Taking into consideration displacment of sapropterin , the Applicant estimated the net drug budget impact over 5 years to be €3.5m. The main drivers of the budget are the number of eligible patients according to the licence and the identified subgroup and the cost of the comparator.

5. Patient submission

A patient organisation submission was received during the course of this assessment from the PKU Association of Ireland. It will be provided to the HSE and form part of the data that the HSE considers.

6. Conclusion

The NCPE recommends that pegvaliase (Palnziq®), for the treatment of patients age 16 years and over with PKU who have inadequate blood phenylalanine control (blood phenylalanine levels over 600 micromol/L) despite prior management with available treatment options, be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments.

**This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.*