Phenylketonuria Prior Authorization Program Summary

Your health benefit plan may not cover certain prescription drug products or drug categories included in this document. Please consult your benefit plan materials for details about your particular benefit. This document may include drugs that are not included on your plan's formulary. For drug coverage status, please consult your plan's formulary.

POLICY REVIEW CYCLE

Effective Date	**Date of Origin**
01-01-2026	

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Kuvan® (sapropterin) Powder for oral solution* Tablet*	Reduce blood phenylalanine (Phe) levels in adult and pediatric patients one month of age and older with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin-(BH4-) responsive phenylketonuria (PKU). Kuvan is to be used in conjunction with a Phe-restricted diet.	*generic available	1
Palynziq® (pegvaliase-pqpz) Subcutaneous injection	To reduce blood phenylalanine concentrations in adult patients with phenylketonuria (PKU) who have uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on existing management		2
Sephience™ (sepiapterin) Oral powder	Treatment of hyperphenylalaninemia (HPA) in adult and pediatric patients 1 month of age and older with sepiapterin-responsive phenylketonuria (PKU). Sephience is to be used in conjunction with a phenylalanine (Phe)-restricted diet.		6

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Phenylketonuria	Phenylketonuria (PKU), also known as phenylalanine hydroxylase (PAH) deficiency, is a rare autosomal recessive error of phenylalanine (Phe) metabolism caused by variants in the gene encoding PAH. PAH deficiency leads to accumulation of Phe in the blood and brain. Untreated, PKU is characterized by irreversible intellectual disability, microcephaly, motor deficits, eczematous rash, autism, seizures, developmental problems, aberrant behavior, and psychiatric symptoms. Since the initiation of newborn screening, almost all cases of PAH deficiency are diagnosed following a positive newborn screening test.(3,4,5) Treatment is recommended to be taken as early as possible, preferably within the first week of life with a goal of having blood Phe in the treatment range within the first 2 weeks of life.(4,5) Dietary therapy, involving dietary Phe restriction and supplementation with reduced or Phe-free amino acid mixtures (medical foods, formulas), is the mainstay of therapy and effective in preventing severe mental retardation association with untreated classical PAH deficiency.(3,4,5)

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	Treatment for life is recommended, even though it is acknowledged that dietary management is associated with significant patient burden.(3,4,5) Over time, subtle intellectual and neuropsychiatric issues may manifest even with treatment.(4) In addition, patients treated from the early weeks of life with initial good metabolic control, but who lose control later in childhood or adult life, may experience both reversible and irreversible neuropsychiatric consequences. Even severely intellectually disabled adults with late-diagnosed PAH deficiency show improvements in challenging behavior with lowering of blood Phe levels.(3,4) Since neurocognitive and neuropsychiatric symptoms, as well as clinically evident neurologic abnormalities including tremor and gait disturbance, are associated with rising Phe levels, the ACMG recommends that treatment for PAH deficiency should be lifelong for individuals with untreated Phe levels greater than 360 microl/L, and that Phe should be maintained less than or equal to 360 micromol/L for life.(4) Sapropterin is a synthetic form of naturally occurring cofactor, tetrahydrobiopterin (BH4) which activates PAH. Some patients with PAH deficiency who have some residual enzyme activity respond to administration of sapropterin with an increase in the metabolism of Phe to tyrosine.(3) Approximately 25-50% of patients with PAH deficiency are sapropterin responsive. A significant decline in blood Phe is expected in responders with the assumption that diet remains stable with sapropterin therapy. Most sapropterin-responsive patients have a rapid decline in blood Phe level, but occasionally a delay of 2-4 weeks is seen.(4) Clinical judgment is required to determine what constitutes as a significant or beneficial blood Phe decline in an individual patient, but 30% is often cited as evidence of effective Phe reduction since clinical trials for sapropterin identified responders as greater than or equal to 30% decrease in blood Phe from baseline.(1,4) Sapropterin treatment is not recommend in patients with two null variants, as response is limited by an absence of residual PAH protein.(3) Sepiapterin is a precursor of the enzymatic cofactor BH4 which activates PAH. Clinical judgment is required to determine what constitutes as a significant or beneficial blood Phe decline in an individual patient, but 30% is often cited as evidence of effective Phe reduction since clinical trials for sepiapterin identified responders as greater than or equal to 30% decrease in blood Phe from baseline.(6) Pegvaliase-pqpz is a phenylalanine-metabolizing enzyme. In adults being treated with pegvaliase, achieving a blood Phe level below 360 micromol/L allows for the possibility of dietary liberalization. After an individual reaches control of blood Phe concentration (less than 360 micromol/L), intact protein is added incrementally while medical food protein is decreased by similar amounts, until dietary reference intake (DRI) is met or exceeded, considering individual needs and preferences.(5,7) Patients should discontinue pegvaliase if they have not achieved an adequate response (i.e., blood phenylalanine concentration less than or equal to 600 micromol/L) after 16 weeks of continuous treatment with the maximum dosage of 60 mg once daily.(2)
Safety	Kuvan (sapropterin) has no FDA labeled contraindications for use.(1) Palynziq (pegvaliase-pqpz) has no FDA labeled contraindications for use, but does have a boxed warning. Anaphylaxis has been reported after administration of pegvaliase-pqpz and may occur at any time during treatment. Auto-injectable epinephrine is prescribed to all patients treated with pegvaliase-pqpz, and the patient (and observer, if applicable) are instructed in recognizing signs and symptoms of anaphylaxis. Due to this, pegvaliase-pqpz is available only through a restricted program called Palynziq REMS.(2) Sephience (sepiapterin) has no FDA labeled contraindications for use.(6)

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REFERENCES

Number	Reference
1	Kuvan prescribing information. BioMarin Pharmaceutical Inc. August 2024.
2	Palynziq prescribing information. BioMarin Pharmaceutical Inc. November 2020.
3	Van Wegberg AMJ, MacDonald A, Ahring K, et al. European guidelines on diagnosis and treatment of phenylketonuria: First revision. Mol Genet Metab. 2025 Jun;145(2):1-41. doi: 10.1016/j.ymgme.2025.109125
4	Smith WE, Berry SA, Bloom K, et al. Phenylalanine hydroxylase deficiency diagnosis and management: A 2023 evidence-based clinical guideline of the American College of Genetics and Genomics (ACMG). Genet Med. 2025 Jan;27(1):1-10. doi: 10.1016/j.gim.2024.101289
5	Genetic Metabolic Dietitians International (GMDI) and Southeast Regional Genetics Network (SERN): PKU nutrition management guidelines. March 2022, v.2.5. Last updated June 2022. Available at: https://managementguidelines.net/guidelines.php/136/overview/0/0/PKU%20Nutrition%20Guidelines/Version%202.5
6	Sephience prescribing information. PTC Therapeutics, Inc. July 2025.
7	Cunningham A, Rohr F, Splett P, et al. Nutrition management of PKU with pegvaliase therapy: Update of the web-based PKU nutrition management guideline recommendations. Orphanet J Rare Dis. 2023 Jun;13:155. doi: 10.1186/s13023-023-02751-0

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Palynziq	pegvaliase-pqpz subcutaneous soln pref syringe	10 MG/0.5ML ; 2.5 MG/0.5ML ; 20 MG/ML	M ; N ; O ; Y	N		
Kuvan	sapropterin dihydrochloride powder packet ; sapropterin dihydrochloride tab	100 MG ; 500 MG	M ; N ; O ; Y	O ; Y		
Sephience	sepiapterin powder packet	1000 MG ; 250 MG	M ; N ; O ; Y	N		

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Kuvan	sapropterin dihydrochloride powder packet ; sapropterin dihydrochloride tab	100 MG ; 500 MG	Accord Enhanced ; Accord Standard ; Choice NetR - A Select ; Choice NetR - F Performance ; Choice NetR-HIM
Palynziq	pegvaliase-pqpz subcutaneous soln pref syringe	10 MG/0.5ML ; 2.5 MG/0.5ML ; 20 MG/ML	Accord Enhanced ; Accord Standard ; Choice NetR - A Select ; Choice NetR - F Performance ; Choice NetR-HIM
Sephience	sepiapterin powder packet	1000 MG ; 250 MG	Accord Enhanced ; Accord Standard ; Choice NetR - A Select ; Choice NetR - F Performance ; Choice NetR-HIM

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

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Module	Clinical Criteria for Approval
PA	**Initial Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of phenylketonuria (PKU) **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. ONE of the following: A. BOTH of the following: 1. Phenylalanine levels cannot be maintained within the recommended maintenance range with dietary intervention (phenylalanine-restriction) despite strict compliance **AND** 2. The Phe-restricted diet will continue while being treated with the requested agent **OR** B. If the requested agent is Palynziq, the patient's current phenylalanine level is less than 360 micromol/L **AND** 4. ONE of the following: A. If the requested agent is Kuvan, sapropterin, or Sephience, the patient has a baseline (prior to therapy for the requested indication) blood Phe level greater than 360 micromol/L **OR** B. If the requested agent is Palynziq, the patient has a baseline (prior to therapy for the requested indication) blood Phe level greater than 600 micromol/L **AND** 5. If the request is for a brand agent, then ONE of the following: A. The patient has tried and had an inadequate response to generic sapropterin despite monitored adherence to treatment **OR** B. The patient has an intolerance or hypersensitivity to generic sapropterin that is NOT expected to occur with the requested brand agent **OR** C. The patient has an FDA labeled contraindication to generic sapropterin that is NOT expected to occur with the requested brand agent **OR** D. There is support for use of the requested brand agent over generic sapropterin (e.g., presence of two null mutations) **AND** 6. The prescriber is a specialist in the area of the patient's diagnosis (e.g., metabolic disorders), or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 7. The patient will NOT be using the requested agent in combination with another phenylketonuria agent (e.g., Kuvan, Palynziq, sapropterin, Sephience) for the requested indication **AND** 8. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 9. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval:** **Kuvan (sapropterin):** Approve for 2 months if initial dose is 5 mg/kg/day to less than 20 mg/kg/day, and for 1 month if initial dose is 20 mg/kg/day **Palynziq (pegvaliase-pqpz):** 9 months **Sephience (sepiapterin):** Approve for 2 months if initial dose is 7.5 mg/kg/day to less than 60 mg/kg/day, and for 1 month if initial dose is 60 mg/kg/day **Renewal Evaluation**

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Module	Clinical Criteria for Approval
	Target Agent(s) will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process (Note: patients not previously approved for the requested agent will require initial evaluation review) **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. ONE of the following: A. The patient is currently on a phenylalanine (Phe) restricted diet and will continue while being treated with the requested agent **OR** B. If the requested agent is Palynziq, the patient's phenylalanine level is less than 360 micromol/L **AND** 4. If the request is for a brand agent, then ONE of the following: A. The patient has tried and had an inadequate response to generic sapropterin despite monitored adherence to treatment **OR** B. The patient has an intolerance or hypersensitivity to generic sapropterin that is NOT expected to occur with the requested brand agent **OR** C. The patient has an FDA labeled contraindication to generic sapropterin that is NOT expected to occur with the requested brand agent **OR** D. There is support for use of the requested brand agent over generic sapropterin (e.g., presence of two null mutations) **AND** 5. The prescriber is a specialist in the area of the patient's diagnosis (e.g., metabolic disorders), or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 6. The patient will NOT be using the requested agent in combination with another phenylketonuria agent (e.g., Kuvan, Palynziq, sapropterin, Sephience) for the requested indication **AND** 7. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 8. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval:** 12 months

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