Phenylketonuria Prior Authorization Program Summary

This program applies to Medicaid.

The BCBS MN Step Therapy Supplement also applies to this program for Medicaid.

Requests for an oral liquid form of a drug must be approved if BOTH of the following apply:

1) the indication is FDA approved AND

2) the patient is using an enteral tube for feeding or medication administration

POLICY REVIEW CYCLE

Effective Date	**Date of Origin**
03-01-2024	

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Kuvan® (sapropterin)* Tablet Oral solution	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). 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. Existing management options include prior or current restriction of dietary phenylalanine and protein intake, and/or prior treatment with sapropterin dihydrochloride.		2

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) There is not

	clear consensus regarding clinical outcomes in treating patients with Phe blood concentrations between 360 and 600 micromol/L, however given the risk for neurocognitive consequences many treatment centers initiate treatment at a Phe level of 360 micromol/L or higher in patients during the first 12 years of life.(3,4) Guidelines recommend patients less than 12 years of age should have target blood Phe between 120 and 360 micromol/L. Patients age 12 or greater with untreated Phe blood concentration greater than 600 micromol/L should be treated. For patients 12 years of age and older, target Phe levels should be 120 to 600 micromol/L.(3) Pregnancy presents a problem in women with PAH deficiency, as high levels of Phe are toxic to the brain of the developing fetus and along with other teratogenic effects, results in a defined maternal PKU syndrome. Treatment should be considered for women prior to conception with blood Phe greater than 360 micromol/L due to risks of maternal PKU.(3,4,5) 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) Sapropterin is a synthetic form of naturally occurring cofactor, tetrahydrobiopterin. 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) Pegvaliase-pqpz is a phenylalanine-metabolizing enzyme. Patients should discontinue pegvaliase-pqpz 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) does not have any contraindications.(1) Palynziq (pegvaliase-pqpz) does not have any contraindications but does carry 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)

REFERENCES

Number	Reference
1	Kuvan prescribing information. BioMarin Pharmaceutical Inc. February 2021.
2	Palynziq prescribing information. BioMarin Pharmaceutical Inc. November 2020.
3	van Wegberg AMJ, MacDonald A, Ahring K, et al. The Complete European Guidelines on Phenylketonuria: Diagnosis and Treatment. Orphanet J Rare Dis. 2017;12(1):162.

Number	Reference
4	Vockley J, Andersson HC, Antshel KM, et al. American College of Medical Genetics and Genomics (ACMG) for Phenylalanine Hydroxylase Deficiency: Diagnosis and Management Guideline. Genet Medicine. 2014;16(2):188–200.
5	Genetic Metabolic Dietitians International (GMDI) and Southeast Regional Genetics Network (SERN): PKU Nutrition Management Guidelines. March 2022 v.2.5 [Updated June 2022]. Available at: https://managementguidelines.net/guidelines.php/136/overview/0/0/PKU%20Nutrition%20Guidelines/Version%202.5/Overview.

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		
Javygtor ; Kuvan	sapropterin dihydrochloride powder packet	100 MG ; 500 MG	M ; N ; O ; Y	O ; Y		
Javygtor ; Kuvan	sapropterin dihydrochloride tab	100 MG	M ; N ; O ; Y	O ; Y		

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Javygtor ; Kuvan	sapropterin dihydrochloride powder packet	100 MG ; 500 MG	Medicaid
Javygtor ; Kuvan	sapropterin dihydrochloride tab	100 MG	Medicaid
Palynziq	pegvaliase-pqpz subcutaneous soln pref syringe	10 MG/0.5ML ; 2.5 MG/0.5ML ; 20 MG/ML	Medicaid

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	INITIAL EVALUATION **Target Agent(s)** will be approved when ONE of the following is met: 1. ALL of the following: A. The patient has a diagnosis of phenylketonuria (PKU) **AND** B. If the patient has an FDA approved indication, then ONE of the following: 1. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** 2. The prescriber has provided information in support of using the requested agent for the patient's age for the requested indication **AND** C. ONE of the following: 1. BOTH of the following: A. Phenylalanine levels cannot be maintained within the recommended maintenance range with dietary intervention (phenylalanine-restriction) despite strict compliance **AND** B. The Phe-restricted diet will continue while being treated with the requested agent **OR** 2. If the requested agent is Palynziq, the patient's current phenylalanine level is less than 360 micromol/L (6 mg/dL) **AND**

Module	Clinical Criteria for Approval
	D. If the requested agent is Kuvan or sapropterin, then ONE of the following: 1. The patient is less than 12 years of age AND has a baseline (prior to therapy for the requested indication) blood Phe level greater than 360 micromol/L (6 mg/dL) **OR** 2. The patient is 12 years of age or over AND has a baseline (prior to therapy for the requested indication) blood Phe level greater than 600 micromol/L (10 mg/dL) **OR** 3. The patient is planning on becoming pregnant OR is currently pregnant AND has a baseline (prior to therapy for the requested indication) Phe level greater than 360 micromol/L (6 mg/dL) **AND** E. 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 (10 mg/dL) **AND** F. If the request is for a brand agent, then ONE of the following: 1. The patient's medication history includes generic sapropterin AND ONE of the following: A. The patient has had an inadequate response to generic sapropterin despite monitored adherence to treatment **OR** B. The prescriber has submitted an evidence-based and peer-reviewed clinical practice guideline supporting the use of the requested agent over generic sapropterin **OR** 2. The patient has an intolerance or hypersensitivity to generic sapropterin that is not expected to occur with the brand agent **OR** 3. The patient has an FDA labeled contraindication to generic sapropterin that is not expected to occur with the brand agent **OR** 4. The prescriber has provided information to support the use of the requested brand agent over generic sapropterin (e.g., presence of two null mutations in trans) **OR** 5. The patient is currently being treated with the requested agent as indicated by ALL of the following: A. A statement by the prescriber that the patient is currently taking the requested agent **AND** B. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent **AND** C. The prescriber states that a change in therapy is expected to be ineffective or cause harm **OR** 6. The prescriber has provided documentation that generic sapropterin cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm **AND** G. 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** H. The patient will NOT be using the requested agent in combination with another targeted agent included in this program **AND** I. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** J. The requested quantity (dose) is within FDA labeled dosing for the requested indication **OR** 2. If the request is for an oral liquid form of a medication, then BOTH of the following: A. The patient has an FDA approved indication **AND** B. The patient uses an enteral tube for feeding or medication administration **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

Module	Clinical Criteria for Approval
	Palynziq (pegvaliase-pqpz): 9 months **RENEWAL EVALUATION** **Target Agent(s)** will be approved when ONE of the following is met: 1. ALL of the following: A. The patient has been previously approved for the requested agent through the plan's Prior Authorization process **AND** B. The patient has had improvements or stabilization with the requested agent as indicated by ONE of the following: 1. If the requested agent is Kuvan or sapropterin, then ONE of the following: A. The patient's blood Phe levels are being maintained within the acceptable range [less than 12 years of age and for females currently pregnant or planning on becoming pregnant: 120-360 micromol/L (2-6 mg/dL); greater than or equal to 12 years of age: 120-600 micromol/L (2-10 mg/dL)] **OR** B. The patient has had at least a 30% decrease in blood Phe level from baseline (prior to therapy for the requested indication) **OR** 2. If the requested agent is Palynziq, then ONE of the following: A. The patient's blood Phe level is less than or equal to 600 micromol/L (10 mg/dL) **OR** B. The patient has had at least a 20% decrease in blood Phe level from baseline (prior to therapy for the requested indication) **OR** C. The patient has NOT received 16 weeks of therapy at the maximum recommended dose in approved labeling AND the prescriber will evaluate for a dose escalation to induce clinical response **AND** C. ONE of the following: 1. The patient is currently on a phenylalanine (Phe) restricted diet and will continue while being treated with the requested agent **OR** 2. If the requested agent is Palynziq, the patient's phenylalanine level is less than 360 micromol/L (6 mg/dL) **AND** D. If the request is for a brand agent, then ONE of the following: 1. The patient's medication history includes generic sapropterin AND ONE of the following: A. The patient has had an inadequate response to generic sapropterin despite monitored adherence to treatment **OR** B. The prescriber has submitted an evidence-based and peer-reviewed clinical practice guideline supporting the use of the requested agent over generic sapropterin **OR** 2. The patient has an intolerance or hypersensitivity to generic sapropterin that is not expected to occur with the brand agent **OR** 3. The patient has an FDA labeled contraindication to generic sapropterin that is not expected to occur with the brand agent **OR** 4. The prescriber has provided information to support the use of the requested brand agent over generic sapropterin (e.g., presence of two null mutations in trans) **OR** 5. The patient is currently being treated with the requested agent as indicated by ALL of the following: A. A statement by the prescriber that the patient is currently taking the requested agent **AND** B. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent **AND** C. The prescriber states that a change in therapy is expected to be ineffective or cause harm **OR** 6. The prescriber has provided documentation that generic sapropterin cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of

Module	Clinical Criteria for Approval
	the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm **AND** E. 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** F. The patient will NOT be using the requested agent in combination with another targeted agent included in this program **AND** G. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** H. The requested quantity (dose) is within FDA labeled dosing for the requested indication **OR** 2. If the request is for an oral liquid form of a medication, then BOTH of the following: A. The patient has an FDA approved indication **AND** B. The patient uses an enteral tube for feeding or medication administration **Length of Approval:** 12 months

