Drug Coverage Policy

Effective Date.....5/1/2026
Coverage Policy Number.....IP0294
Policy Title.....Palynziq

Phenylketonuria – Palynziq

- Palynziq® (pegvaliase-pqpz subcutaneous injection – BioMarin)

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

OVERVIEW

Palynziq, a phenylalanine-metabolizing enzyme, is indicated to reduce blood phenylalanine concentrations in patients ≥ 12 years of age with **phenylketonuria (PKU)** who have uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on existing management.[1]

Treatment with Palynziq should be managed by a healthcare provider experienced in the management of PKU. Baseline blood phenylalanine concentrations should be obtained before initiating treatment. Because of the risk of anaphylaxis, Palynziq is available only through a restricted Risk Evaluation and Mitigation Strategy (REMS) program.[1]

Dose Titration
The recommended initial induction dosage for Palynziq is 2.5 mg subcutaneously (SC) for 4 weeks.[1] This dose is then titrated over a period of at least 5 weeks to a maintenance dose of 20 mg SC once daily (QD). The maintenance dose should be individualized to achieve blood phenylalanine control (blood phenylalanine concentration ≤ 600 micromol/L). Maintain the Palynziq 20 mg QD dose for at least 24 weeks. Consider increasing the Palynziq dose to 40 mg QD in a patient who has been on 20 mg QD for at least 24 weeks without achieving blood phenylalanine control. Consider increasing the Palynziq dose to a maximum of 60 mg QD in a patient who has been on 40 mg QD for at least 16 weeks without achieving blood phenylalanine control. Discontinue Palynziq in a patient who has not achieved an adequate response after continuous treatment with the maximum dose of 60 mg QD for 16 weeks. A dose titration schedule is outlined in Table 1. Therapeutic response may not be achieved until the patient is titrated to an effective maintenance dose.

Table 1. Palynziq Dose Titration.[1]

Treatment	Palynziq Dose	Duration*
Induction	2.5 mg once weekly	4 weeks
Titration	2.5 mg twice weekly	1 week
	10 mg once weekly	1 week
	10 mg twice weekly	1 week
	10 mg four times weekly	1 week
	10 mg QD	1 week
Maintenance	20 mg QD	24 weeks
	40 mg QD	16 weeks
Maximum	60 mg QD	16 weeks
Total	--	**65 weeks**

* Additional time may be required prior to each dosage escalation based on patient tolerability; QD – Once daily.

It was unclear from the Palynziq clinical trials if all patients had tried and were non-responders to sapropterin.

Disease Overview
PKU or phenylalanine hydroxylase (PAH) deficiency is an autosomal recessive disorder caused by pathogenic variants in the *PAH* gene.[2] PAH converts phenylalanine (Phe) to tyrosine and requires the co-substrate tetrahydrobiopterin (BH_4). With PAH deficiency, Phe can accumulate and lead to brain dysfunction resulting in severe intellectual disability, epilepsy, and behavioral problems. The incidence of PKU in the United States is approximately 1 in 25,000, which equates to approximately 13,600 individuals living with PKU.[3]

Guidelines
A consensus statement regarding use of Palynziq in adults with PKU was published in 2019.[4] Palynziq should be considered for all adults with PKU who have the ability to give informed consent and adhere to treatment. It is noted that some patients may show a response early on, whereas others may take 1 year or more from initiation of treatment before a reduction in blood Phe concentration is observed. The definition of a "clinically meaningful" efficacy benefit should be determined by the treating clinician based on individual patient goals. Primarily, the efficacy benefit should be determined by a significant reduction in blood Phe concentration from baseline.

In 2023 the American College of Medical Genetics and Genomics (ACMG) updated their practice guidelines for the diagnosis and management of Phe hydroxylase (PAH) deficiency.[5] ACMG recommends treating individuals with blood Phe levels greater than 360 µmol/L and maintaining Phe levels to ≤ 360 µmol/L for life as it is associated with higher IQ levels. ACMG advocates combination of therapies (e.g., dietary restriction, use of medical foods that are Phe-free or low in Phe, sapropterin, Palynziq) and individualization of treatment to improve blood Phe levels. Therapy resulting in a reduction of blood Phe, increase in dietary Phe tolerance, or improvement in clinical symptoms should be continued. Due to insufficient evidence, ACMG does not recommend nor discourage the use of Palynziq in pregnant individuals with PAH deficiency to prevent negative gestational outcomes or negative outcomes for the offspring.

European guidelines (2025) are available for diagnosis and management of PKU.[6] The guidelines classify PKU as either not requiring treatment (Phe < 360 µmol/L), requiring treatment and co-factor (i.e., sapropterin) responsive, or requiring treatment and co-factor non-responsive. Early treatment is advocated (ideally before 10 days of age), and children < 12 years of age should aim for a Phe level of 120 to 360 µmol/L. However, unlike the US guidelines, the target level for children ≥12 to 18 years old and for adults > 18 years old is higher at 120 to 600 µmol/L (except in pregnancy where the target level is 120 to 360 µmol/L). Palynziq is recommended for patients with PKU > 16 years of age (European Medicines Agency approved age for pegvaliase is 16 years of age and older) for those who are unable to achieve metabolic control with sapropterin. They also note that, due to a lack of data, Palynziq is currently not recommended during pregnancy or for women in the preconception period.

Coverage Policy

POLICY STATEMENT

Prior Authorization is required for benefit coverage of Palynziq. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Palynziq as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Palynziq to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Palynziq is considered medically necessary when the following are met:

FDA-Approved Indication

1. **Phenylketonuria.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
     - **i.** Patient is ≥ 12 years of age; AND
     - **ii.** Patient has uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on at least one existing treatment modality; AND
       Note: Examples of treatment modalities include restriction of dietary phenylalanine and protein intake and prior treatment with sapropterin (Kuvan, Javygtor, Zelvysia, generic) or Sephience.
     - **iii.** The medication is prescribed by, or in consultation with, a metabolic disease specialist, or specialist who focuses in the treatment of metabolic diseases; OR
   - **B)** Patient is Currently Receiving Palynziq. Approve for 1 year if the patient meets BOTH of the following (i and ii):
     Note: A patient who has received < 1 year of therapy or who is restarting therapy with Palynziq should be considered under Initial Therapy criteria.
     - **i.** Patient is ≥ 12 years of age; AND

ii. Patient meets ONE of the following (a or b):
- **a)** Patient meets BOTH of the following (1 and 2):
  - **(1)** According to the prescriber, the patient is continuing to titrate Palynziq to a stable maintenance dose; AND
  - **(2)** If the patient is receiving a dose of Palynziq 60 mg once daily, the treatment duration at this dose has not exceeded 16 weeks; OR
- **b)** Patient is on stable maintenance dosing and meets BOTH of the following (1 and 2):
  - **(1)** Patient meets ONE of the following (a or b):
    - **(a)** Patient has achieved blood phenylalanine concentrations ≤ 600 micromol/L; OR
    - **(b)** Patient has achieved a ≥ 20% reduction in blood phenylalanine concentration from pre-treatment baseline (i.e., blood phenylalanine concentration before starting Palynziq therapy); AND
  - **(2)** Patient is not receiving concomitant therapy with sapropterin (Kuvan, Javygtor, Zelvysia, generic) or Sephience (sepiapterin).

Conditions Not Covered

Palynziq for any other use is considered not medically necessary. Criteria will be updated as new published data are available.

References

1. Palynziq™ subcutaneous injection [prescribing information]. Novato, CA: BioMarin; February 2026.
2. van Spronsen FJ, Blau N, Harding C, et al. Phenylketonuria. *Nat Rev Dis Primers*. 2021;7(1):36.
3. Hillert A, Anikster Y, Belanger-Quintana A, et al. The genetic landscape and epidemiology of phenylketonuria. *Am J Hum Genet*. 2020;107:234-250.
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 Medical Genetics and Genomics (ACMG). *Genet Med*. 2025 Jan;27(1):101289.
5. van Wegberg AMJ, MacDonald A, Ahring K, et al. European guidelines on diagnosis and treatment of phenylketonuria: First revision. *Mol Genet Metab*. 2025;145:109125.
6. Longo N, Dimmock D, Levy H, et al. Evidence- and consensus-based recommendations for the use of pegvaliase in adults with phenylketonuria. *Genet Med*. 2019 Aug;21(8):1851-1867.

Revision Details

Summary of Changes	Review Date	Effective Date
Phenylketonuria (PKU): **Removed** the requirement for Palynziq to be prescribed in in conjunction with a phenylalanine restricted diet. **Removed** the no concomitant use with sapropterin (Kuvan), once stabilized on Palynziq. This requirement has been moved to the reauthorization criteria. **Reauthorization Criteria:** **Added** a statement limiting the treatment duration, at a dose of 60 mg, to 16 weeks.	9/26/2024	11/15/2024

Added a statement prohibiting concomitant therapy with sapropterin (Kuvan).		
Policy Title. **Updated** from "Pegvaliase-pqpz" **to** "Phenylketonuria – Palynziq" **Phenylketonuria** **Removed** "Documented diagnosis of phenylketonuria (PKU) confirmed by documentation of ONE of the following: A. Plasma phenylalanine concentration persistently above 120 µmol/L (2 mg/dL) and altered ratio of phenylalanine to tyrosine in the untreated state with normal BH4 cofactor metabolism B. Molecular genetic test demonstrating biallelic pathogenic or likely pathogenic variants in the PAH gene." **Updated** from "Documentation of uncontrolled blood phenylalanine concentrations of greater than 600 micromol/L on existing management (for example, phenylalanine restricted diet, sapropterin [Kuvan])" **to** "Patient has uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on at least one existing treatment modality; AND Note: Examples of treatment modalities include restriction of dietary phenylalanine and protein intake and prior treatment with sapropterin (Kuvan, Javygtor, generic)" **Updated** from "Blood phenylalanine levels are being maintained within an acceptable range (120-600 µmol/L) " **to** "Patient's blood phenylalanine concentration is ≤ 600 micromol/L" **Updated** from "Patient is not receiving concomitant therapy with sapropterin (Kuvan)" **to** "Patient is not receiving concomitant therapy with sapropterin (Kuvan, Javygtor, generic)"	9/4/2025	11/01/2025
Phenylketonuria: For Initial Therapy, Zelvysia (sapropterin powder for oral solution) and Sephience (sepiapterin oral powder) were added to the Note as examples of treatment modalities. For a patient continuing therapy with Palynziq, "patient is continuing to titrate Palynziq to an effective maintenance dose, per the prescriber" was changed to "according to the prescriber, the patient is continuing to titrate Palynziq to a stable maintenance dose." Clarified that the response criteria apply to a patient on stable maintenance dosing of Palynziq with no concurrent use of sapropterin; Zelvysia was added as an example of a sapropterin product and Sephience was added.	11/13/2025	01/15/2026

Phenylketonuria: For Initial Therapy and Patient is Currently Receiving Palynziq, the age requirement was changed to ≥ 12 years of age.	3/26/2026	5/1/2026

The policy effective date is in force until updated or retired.