# Drug Coverage Policy

**Effective Date……9/15/2026**
**Coverage Policy Number……IP0294**
**Policy Title……Palynziq**

# Phenylketonuria – Palynziq

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

***INSTRUCTIONS FOR USE***

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**OVERVIEW**

Palynziq, a phenylalanine-metabolizing enzyme, is indicated to reduce blood phenylalanine (Phe) concentrations in patients ≥ 12 years of age with **phenylketonuria (PKU)** who have uncontrolled blood Phe concentrations > 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 Phe 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 program.[1]

**Dose Titration**
The recommended initial induction dosage for Palynziq is 2.5 mg subcutaneously (SC) once weekly 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 Phe control (blood Phe 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 Phe 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 Phe 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 Phe to tyrosine and requires the co-substrate tetrahydrobiopterin. 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):**<br>**Removed** the requirement for Palynziq to be prescribed in in conjunction with a phenylalanine restricted diet.<br>**Removed** the no concomitant use with sapropterin (Kuvan), once stabilized on Palynziq. This requirement has been moved to the reauthorization criteria.<br><br>**Reauthorization Criteria:**<br>**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.**<br>**Updated** from "Pegvaliase-pqpz" **to** "Phenylketonuria – Palynziq"<br><br>**Phenylketonuria**<br>**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."<br><br>**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)"<br><br>**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"<br><br>**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 |

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|---|---|---|
| **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 |
| No criteria changes. | 9/3/2026 | 9/15/2026 |

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

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