PRIOR AUTHORIZATION POLICY

POLICY: Phenylketonuria – Palynziq Prior Authorization Policy
- Palynziq® (pegvaliase-pqpz subcutaneous injection – BioMarin)

REVIEW DATE: 08/28/2024

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 AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. 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.

CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

Palynziq, a phenylalanine-metabolizing enzyme, is indicated 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.[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.

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.

Guidelines

Recommendations regarding use of Palynziq are not made in guidelines from the American College of Medical Genetics and Genomics (ACMG) [2014] or European guidelines (2017).[2,3] However, 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 other may take 1 year or more from initiation of treatment before a reduction in blood phenylalanine 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 phenylalanine concentration from baseline.

Although ACMG and European guidelines do not offer recommendations specific to Palynziq, they do provide general principles for PKU management. ACMG guidelines suggest a target blood phenylalanine level of 120 to 360 micromol/L for all patients.[2] However, European guidelines state that patients ≥ 12 years of age with blood phenylalanine concentration < 600 micromol/L do not require treatment, and the target range for patients ≥ 12 years of age receiving treatment is 120 to 600 micromol/L.[3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Palynziq. 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. All approvals are provided for the duration noted below.

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

is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):

of Palynziq is recommended in those who meet the following criteria:

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 ≥ 18 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, generic).
     - **iii.** The medication is prescribed by or in consultation with a metabolic disease specialist (or specialist who focuses in the treatment of metabolic diseases).
   - **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 ≥ 18 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)** Patient is continuing to titrate Palynziq to an effective maintenance dose, per the prescriber; 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 meets BOTH of the following (1 and 2):
         - **(1)** Patient meets ONE of the following (a or b):
           - **(a)** Patient's blood phenylalanine concentration is ≤ 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, generic).

CONDITIONS NOT COVERED

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

is(are) considered experimental, investigational or unproven for ANY other use(s); criteria will be updated as new published data are available).

REFERENCES

1. Palynziq™ subcutaneous injection [prescribing information]. Novato, CA: BioMarin; November 2020.
2. Vockley J, Andersson HC, Antshel KM, et al; American College of Medical Genetics and Genomics Therapeutics Committee. Phenylalanine hydroxylase deficiency: diagnosis and management guideline. *Genet Med*. 2014 Feb;16(2):188-200.
3. van Wegberg AMJ, MacDonald A, Ahring A, et al. The complete European guidelines on phenylketonuria: diagnosis and treatment. *Orphanet J Rare Dis.* 2017;12:162.
4. 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.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	08/23/2023
Annual Revision	No criteria changes.	08/28/2024