Effective Date **1/15/2024**
Next Review Date… **1/15/2025**
Coverage Policy Number **IP0294**

Pegvaliase-pqpz

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Related Coverage Resources

INSTRUCTIONS FOR USE
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Overview

This policy supports medical necessity review for pegvaliase-pqpz subcutaneous injection (**Palynziq®**).

Receipt of sample product does not satisfy any criteria requirements for coverage.

Medical Necessity Criteria

Pegvaliase-pqpz (Palynziq) is considered medically necessary when the following are met:

Phenylketonuria (PKU). Individual meets **ALL** of the following criteria:
A. Age 18 years or older
B. Documented diagnosis of phenylketonuria (PKU) confirmed by documentation of **ONE** of the following:
    i. 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

ii. Molecular genetic test demonstrating biallelic pathogenic or likely pathogenic variants in the *PAH* gene

C. Documentation of uncontrolled blood phenylalanine concentrations of greater than 600 micromol/L on existing management (for example, phenylalanine restricted diet, sapropterin [Kuvan])
D. Palynziq is prescribed in conjunction with a phenylalanine restricted diet
E. No concomitant use with sapropterin (Kuvan), once stabilized on Palynziq
F. Medication is prescribed by, or in consultation with, a metabolic disease specialist, or specialist who focuses in the treatment of metabolic diseases

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When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Reauthorization Criteria

Continuation of Pegvaliase-pqpz (Palynziq) is considered medically necessary for the treatment of Phenylketonuria (PKU) when **ALL** of the following are met:

1. The above medical necessity criteria have been met prior to the start of Palynziq therapy
2. Blood phenylalanine levels are being maintained within an acceptable range (120-600 µmol/L)
3. Individual has achieved a greater than or equal to 20% reduction in blood phenylalanine concentration from pre-treatment baseline
4. Is continuing to titrate Palynziq to an effective maintenance dose of up to 60 mg daily

Authorization Duration

Initial approval duration: up to 12 months.
Reauthorization approval duration: up to 12 months.

Conditions Not Covered

Any other use is considered experimental, investigational or unproven.

Background

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.

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.

Because of the risk of anaphylaxis Palynziq is available only through a restricted Risk Evaluation and Mitigation Strategy (REMS) program. 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]

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.