

pegvaliase-pqpz (Palynziq™)

Policy # 00644

Original Effective Date: 11/21/2018

Current Effective Date: 12/01/2025

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider pegvaliase-pqpz (Palynziq™)[‡] for the treatment of phenylketonuria (PKU) to be **eligible for coverage**.^{**}

Patient Selection Criteria

Coverage eligibility for pegvaliase-pqpz (Palynziq) will be considered when the following criteria are met:

Initial Authorization for the Titration Phase (Up to 20 mg Once Daily):

- Patient has a diagnosis of phenylketonuria; AND
- Patient is 18 years of age or older; AND
- Patient's phenylalanine concentration is currently greater than 600 micromol/L on existing management (e.g., dietary restrictions, treatment with phenylalanine hydroxylase [PAH] activators such as sapropterin [Kuvan®, generics][‡] or sepiapterin [Sephience™][‡]); AND
- Patient is NOT using the requested drug in combination with sapropterin (Kuvan, generics) or sepiapterin (Sephience).

Re-authorization for 20 mg Once Daily:

- Initial criteria were met; AND
- Patient's blood phenylalanine concentrations are LESS than or EQUAL to 600 micromol/L on the 20 mg once daily dosage.

Request for 40 mg Once Daily:

- Initial criteria were met; AND
- Patient has NOT achieved blood phenylalanine concentrations LESS than or EQUAL to 600 micromol/L after at least 24 weeks of therapy on the 20 mg once daily dosage.

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Re-authorization for 40 mg Once Daily:

- Initial criteria were met; AND
- Patient's blood phenylalanine concentrations are LESS than or EQUAL to 600 micromol/L after at least 16 weeks of therapy on the 40 mg once daily dosage.

Request for 60 mg Once Daily:

- Initial criteria were met; AND
- Patient has NOT achieved blood phenylalanine concentrations LESS than or EQUAL to 600 micromol/L after at least 16 weeks of therapy on the 40 mg once daily dosage.

Re-authorization for 60 mg Once Daily:

- Initial criteria were met; AND
- Patient's blood phenylalanine concentrations are LESS than or EQUAL to 600 micromol/L after at least 16 weeks of therapy on the 60 mg once daily dosage.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of pegvaliase-pqpz (Palynziq) when the patient selection criteria are NOT met to be **investigational**.*

Background/Overview

Palynziq is a phenylalanine-metabolizing enzyme 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. Palynziq is a pegylated phenylalanine ammonia lyase enzyme that converts phenylalanine to ammonia and trans-cinnamic acid. It substitutes for the deficient phenylalanine hydroxylase enzyme activity in patients with phenylketonuria and reduces blood phenylalanine concentrations. Before initiating treatment, blood phenylalanine levels should be obtained. The recommended initial dosage is 2.5 mg subcutaneously once weekly for 4 weeks. The dose should then be titrated in a step-wise manner over at least 5 weeks based on tolerability to achieve a dosage of 20 mg subcutaneously once daily. The 20 mg subcutaneous dose can be maintained if the patient has achieved phenylalanine concentrations of less than or equal to 600 micromol/L. If the patient hasn't achieved phenylalanine concentrations of less than or equal to 600 micromol/L after at least 24 weeks of the 20 mg subcutaneous once daily dosage, the dose should be increased to 40 mg subcutaneous once daily. If the patient hasn't achieved phenylalanine concentrations of less than or equal to 600 micromol/L after at least 16 weeks of the 40 mg subcutaneous once daily dosage, the dose should be increased to 60 mg subcutaneous once daily. Palynziq should be discontinued in patients that have NOT achieved phenylalanine concentrations of less than or equal to 600 micromol/L after 16 weeks of therapy with the 60 mg subcutaneous dose.

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Phenylketonuria

Phenylketonuria affects the amino acid, phenylalanine. This autosomal recessive disorder arises from a deficiency of phenylalanine hydroxylase. If left untreated, the condition can lead to intellectual disability. The exact mechanism is unknown for the cause of intellectual disability, but it is thought that the excessive levels of phenylalanine interfere with brain growth and other neurological factors. The mainstay of therapy for PKU involves dietary restriction of phenylalanine, which is present in most protein sources. If dietary management fails to maintain blood phenylalanine levels ≤ 360 micromol/L, drug therapy may be required in addition to dietary modifications. Pharmacological therapy for PKU includes oral phenylalanine hydroxylase (PAH) activators such as sapropterin (Kuvan, generics) and sepiapterin (Sephience). Sapropterin is a co-factor for the phenylalanine hydroxylase enzyme, which assists the enzyme in its purpose. Sepiapterin is a precursor of the enzymatic co-factor tetrahydrobiopterin (BH4) which may activate residual PAH enzyme activity. In comparison, Palynziq is an enzyme substitution therapy. The active ingredient in Palynziq converts phenylalanine to ammonia and trans-cinnamic acid, which are metabolized by the liver and excreted in the urine.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Palynziq is a phenylalanine-metabolizing enzyme indicated to reduce blood phenylalanine concentrations in adult patients with phenylketonuria who have uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on existing management.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

Induction/Titration/Maintenance

The efficacy and safety of Palynziq was studied (Study 301), in an open label randomized, multi-center study of adults with PKU. This study evaluated an induction/titration/maintenance regimen with a target maintenance dose of 20 mg subcutaneously once daily or 40 mg subcutaneously once daily. At Palynziq treatment initiation, 253 patients demonstrated inadequate blood phenylalanine control (blood phenylalanine concentration greater than 600 micromol/L) on existing management, and 8 patients had blood phenylalanine concentrations less than or equal to 600 micromol/L. Existing management options included prior or current restriction of dietary phenylalanine and protein intake, and/or prior treatment with Kuvan. Patients previously treated with Kuvan were required to discontinue use at least 14 days prior to the first dose.

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The 261 enrolled patients were aged 16 to 55 years and had a baseline mean blood phenylalanine of 1,233 micromol/L. Patients were randomized (1:1) to one of two target maintenance dosage arms: 20 mg once daily or 40 mg once daily. Patients were titrated to reach their randomized target dosage of 20 mg once daily or 40 mg once daily. The duration of titration varied among patients and was based on patient tolerability. Of the 261 enrolled patients, 195 (75%) patients reached their randomized maintenance dosage (103 in the 20 mg once daily arm, 92 in the 40 mg once daily arm). Among the patients who reached their randomized maintenance dosage, patients in the 20 mg once daily randomized arm reached their maintenance dosage at a median time of 10 weeks (range: 9 to 29 weeks) and patients in the 40 mg once daily arm reached their maintenance dosage at a median time of 11 weeks (range: 10 to 33 weeks).

Of the 261 patients who enrolled in Study 301, 54 (21%) patients discontinued treatment during Study 301, 4 patients completed Study 301 and did not continue to Study 165-302 (referred to as Study 302, NCT01889862), 152 patients continued to the eligibility period of Study 302, and 51 patients continued directly from Study 301 into the long-term treatment period of Study 302.

Efficacy Assessment

A total of 164 adult patients with PKU who were previously treated with Palynziq (152 patients from Study 301 and 12 patients from other Palynziq trials) enrolled in Study 302 and continued treatment with Palynziq in Study 302 for up to 13 weeks to assess eligibility for randomized withdrawal period. Following this period of up to 13 weeks of additional Palynziq treatment in Study 302, eligibility for entry into the efficacy assessment period (randomized withdrawal period) was determined by whether a patient achieved at least a 20% reduction in blood phenylalanine concentration from pre-treatment baseline (when in previous studies). Eighty-six out of 164 patients (52%) met this response target and continued into the randomized withdrawal period. In the double-blind, placebo-controlled, randomized withdrawal period, patients were randomized in a 2:1 ratio to either continue their maintenance Palynziq dosage or to receive matching placebo for a total of 8 weeks. The treatment difference between the Palynziq and placebo groups in the mean change in the blood phenylalanine concentration from randomized discontinuation time baseline to week 8 was statistically significant. At week 8, the least square mean change treatment difference in blood phenylalanine concentration was -973.0 µmol/L between the Palynziq 20 mg treatment group and the placebo 20 mg group ($P < 0.0001$). Likewise, the treatment difference was -588.5 µmol/L between the Palynziq 40 mg treatment group and the placebo 40 mg group ($P < 0.0001$).

Continuous Treatment

Of 118 patients from Study 301 with a pre-treatment baseline blood phenylalanine concentration greater than 600 micromol/L who were randomized to and received at least one dose of 20 mg once daily Palynziq, 107 patients, 97 patients, 93 patients, 86 patients, and 77 patients were treated for at least 6 months, 12 months, 18 months, 24 months, and 36 months, respectively. During the continuous treatment period, patients were allowed to dose up to 60 mg once daily based on investigator discretion to achieve blood phenylalanine lowering (for example, to achieve blood phenylalanine concentrations between 120 and 360 micromol/L). Of the 118 patients, a majority (91 patients, 77%) reached their first response, defined as a blood phenylalanine concentration less than

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or equal to 600 micromol/L, at a time point prior to 36 months. Of the 91 patients, 9 patients (10%) achieved their first response at a dose less than 20 mg once daily, 44 patients (48%) achieved their first response at a dose of 20 mg once daily, 26 patients (29%) achieved their first response at a dose of 40 mg once daily, and 12 patients (13%) achieved their first response at a dose of 60 mg once daily. Of the 44 patients that achieved their first response at a dose of 20 mg once daily, 36 (82%) achieved it by 24 weeks of treatment. Of the 26 patients that achieved their first response at a dose of 40 mg once daily, 18 (69%) achieved it by 16 weeks of treatment. Of the 12 patients that achieved their first response at a dose of 60 mg once daily, 8 (67%) achieved it by 16 weeks of treatment.

Of the 107 patients treated for at least 6 months, 28 (26%), 18 (17%), and 11 (10%) had a blood phenylalanine concentration less than or equal to 600, 360, and 120 micromol/L, respectively, at 6 months of treatment. Of the 97 patients treated for at least 12 months, 47 (48%), 41 (42%), and 31 (32%) had a blood phenylalanine concentration less than or equal to 600, 360, and 120 micromol/L, respectively, at 12 months of treatment. Of the 93 patients treated for at least 18 months, 64 (69%), 46 (49%), and 36 (39%) had a blood phenylalanine concentration less than or equal to 600, 360, and 120 micromol/L, respectively, at 18 months of treatment. Of the 86 patients treated for at least 24 months, 65 (76%), 57 (66%), and 43 (50%) had a blood phenylalanine concentration less than or equal to 600, 360, and 120 micromol/L, respectively, at 24 months of treatment. Of the 77 patients treated for at least 36 months, 58 (75%), 51 (66%), and 37 (48%) had a blood phenylalanine concentration less than or equal to 600, 360, and 120 micromol/L, respectively, at 36 months of treatment.

References

1. Palynziq [package insert]. BiMarin Pharmaceutical Inc. Novato, California. November 2020.
2. Palynziq Drug Evaluation. Express Scripts. Updated June 2018.
3. Overview of Phenylketonuria. UpToDate. Updated June 2016.
4. Sephience [package insert]. PTC Therapeutics, Inc. Warren, New Jersey. Updated July 2025.

Policy History

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11/08/2018	Medical Policy Committee review
11/21/2018	Medical Policy Implementation Committee approval. New policy.
11/07/2019	Medical Policy Committee review
11/13/2019	Medical Policy Implementation Committee approval. No change to coverage.
11/05/2020	Medical Policy Committee review
11/11/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/04/2021	Medical Policy Committee review

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- 11/10/2021 Medical Policy Implementation Committee approval. Updated the policy with the new dosing from the FDA package insert. Removed the language regarding at least a 20% reduction in blood phenylalanine concentration from treatment baseline for continuation of dosing based on FDA package insert changes.
- 11/03/2022 Medical Policy Committee review
- 11/09/2022 Medical Policy Implementation Committee approval. No change to coverage.
- 11/02/2023 Medical Policy Committee review
- 11/08/2023 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 11/07/2024 Medical Policy Committee review
- 11/13/2024 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 11/06/2025 Medical Policy Committee review
- 11/12/2025 Medical Policy Implementation Committee approval. Updated criterion requiring that Palynziq will not be used in combination with the new product, Sephience. Updated background information.

Next Scheduled Review Date: 11/2026

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 - 1. Consultation with technology evaluation center(s);
 - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 - 3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

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- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.