pegvaliase-pqpz (Palynziq™)

Policy # 00644
Original Effective Date: 11/21/2018
Current Effective Date: 12/14/2020

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 sapropterin [Kuvan®‡]); AND
- Member is NOT using the requested drug in combination with sapropterin (Kuvan).

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 OR patient has achieved GREATER than or EQUAL to a 20% reduction in blood phenylalanine concentration from pegvaliase-pqpz (Palynziq) treatment baseline.

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 OR patient has NOT achieved GREATER than or EQUAL to a 20% reduction

in blood phenylalanine concentration from pegvaliase-pqpz (Palynziq) treatment baseline after at least 24 weeks of therapy on the 20 mg once daily dosage.

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 OR patient has achieved GREATER than or EQUAL to a 20% reduction in blood phenylalanine concentration from pegvaliase-pqpz (Palynziq) treatment baseline after at least 16 weeks of therapy on the 40 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 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 OR if the patient has achieved at least a 20% reduction in blood phenylalanine concentration from pre-treatment baseline. If the patient hasn't met these treatment goals after at least 24 weeks of the 20 mg subcutaneous once daily dosage, the dose should be increased to 40 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 OR if the

patient has NOT achieved at least a 20% reduction in blood phenylalanine concentration from pre-treatment baseline on the 40 mg subcutaneous dose.

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. Typical treatment of phenylketonuria involves dietary restriction. Only one other pharmacologic therapy exists for this condition in Kuvan. Kuvan is a factor for the phenylalanine hydroxylase enzyme, which assists the enzyme in its purpose. 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. FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal 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.

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, 108 patients, 98 patients, and 51 patients were treated for at least 24 weeks, 48 weeks, and 96 weeks, respectively.

Of the 118 patients, 53 patients reached their first response (at least a 20% reduction in blood phenylalanine concentration from pre-treatment baseline or a blood phenylalanine concentration less than or equal to 600 micromol/L) by 4 weeks of treatment with 20 mg once daily and 28 patients reached their first response between Weeks 4 and 24 with 20 mg once daily. Of the 118 patients, 25 patients escalated their dosage from 20 mg once daily to 40 mg once daily before reaching a first response; of those 25 patients, 8 patients reached their first response by 4 weeks of treatment with 40 mg once daily and 6 patients reached their first response between Weeks 4 and 16 with 40 mg once daily.

References

1. Palynziq [package insert]. Biomarin Pharmaceutical Inc. Novato, California. May 2018.
2. Palynziq Drug Evaluation. Express Scripts. Updated June 2018.
3. Overview of Phenylketonuria. UpToDate. Updated June 2016.

Policy History

Original Effective Date: 11/21/2018
Current Effective Date: 12/14/2020

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.

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11/05/2020 Medical Policy Committee review
11/11/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Next Scheduled Review Date: 11/2021

*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 the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated 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
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.