Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCEND054.0426	**ENDOCRINE AND METABOLIC DRUGS** **PHENYLALANINE-LOWERING THERAPIES FOR PHENYLKETONURIA** See Table 1 for Applicable Medications
Effective Date: 6/1/2026	**Review/Revised Date**: 09/18, 03/19, 02/20, 02/21, 02/22, 03/23, 02/24, 02/25, 03/26 (NN/MTW)
Original Effective Date: 01/19	**P&T Committee Meeting Date**: 10/18, 04/19, 04/20, 04/21, 04/22, 04/23, 04/24, 04/25, 04/26
Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as “Company” and collectively as “Companies”).

APPLIES TO:
Commercial
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
For initial authorization, both of the following criteria must be met:
1. Diagnosis of phenylketonuria (PKU)
2. One of the following:
    a. For **Palynziq**: Documentation of blood phenylalanine concentration more than 600 micromol/L (10 mg/dL) despite management with dietary phenylalanine restriction and sapropterin
    b. For **Sephience**: Both of the following:
        i. Documentation of failure with sapropterin in combination with dietary phenylalanine restriction. Failure is defined as blood phenylalanine concentration more than 360 micromol/L (10 mg/dL).
        ii. Medication will be used in conjunction with a phenylalanine (Phe)-restricted diet

For reauthorization for **Palynziq**, one of the following criteria must be met:
1. Documentation that blood phenylalanine concentration levels have decreased by at least 20% from baseline and remain at least 20% below pretreatment baseline, OR

2. Documentation of a blood phenylalanine concentration less than or equal to 600 micromol/L (10 mg/dL), OR
3. For those not on maximum allowed dose of 60 mg once daily: Authorization for six months may be approved for those who have not met blood phenylalanine control when there is a documented plan for further dose increase up to a maximum dose of 60 mg once daily

   Note: Prescribing information recommends considering dose increase in those you have been on pegvaliase 20 mg daily for at least 24 weeks or 40 mg daily for at least 16 weeks and have not met blood phenylalanine control, up to a maximum dose of 60 mg once daily.

For reauthorization for **Sephience**: both of the following must be met:

1. Documentation that blood phenylalanine concentration levels have decreased by at least 15% from baseline (prior to initiating therapy) and remain at least 15% below pretreatment baseline OR member has maintained blood phenylalanine concentrations less than 360 micromol/L
2. Medication will be used in conjunction with a phenylalanine (Phe)-restricted diet

EXCLUSION CRITERIA:
Use in combination with another drug for phenylketonuria, such as sapropterin (Kuvan), Palynziq, or Sephience.

AGE RESTRICTIONS:
Palynziq: Approved for 18 years and older.

PRESCRIBER RESTRICTIONS:
Initial authorization and reauthorization: Must be prescribed by, or in consultation with, a metabolic disease specialist or a provider who specializes in the treatment of phenylketonuria (PKU).

COVERAGE DURATION:
Palynziq: Initial authorization will be approved for six months.
Sephience: Initial authorization will be approved for one month.

Reauthorization will be approved for one year.

QUANTITY LIMIT:

- Palynziq
  - 2.5 MG/0.5 ML: eight syringes per 28 days

  - 10 MG/0.5 ML: one syringe per day
  - 20 MG/1 ML: three syringes per day
- Sephience
  - 250 mg packets: three packets per day

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Pegvaliase (Palynziq) is a PEGylated recombinant phenylalanine ammonia lyase enzyme that targets the underlying cause of phenylketonuria (PKU) by helping the body to break down phenylalanine. It is administered as a subcutaneous injection. Initial dose is 2.5 mg subcutaneous once weekly for four weeks, then up-titrated once weekly, as tolerated, by to achieve goal dose of 20 mg once daily for at least 24 weeks, then the dose can be further titrated to maximum dose of 60 mg subcutaneous once daily.

Sepiapterin (Sephience) is a precursor of the enzymatic co-factor tetrahydrobiopterin (BH_4) which activates phenylalanine hydroxylase (PAH). It is an oral powder with weight based dosing for individuals less than two years old, with standard maximum dosing of 60 mg/kg for ages two years and older.

FDA APPROVED INDICATIONS:

Table 1.

Brand name	Generic name	FDA indication
Palynziq	pegvaliase-pqpz	Reduce blood phenylalanine concentrations in adult and pediatric patients 12 years of age and older with phenylketonuria (PKU) who have uncontrolled blood

		phenylalanine concentrations greater than 600 micromol/L on existing management
Sephience	Sepiapterin	Treatment of hyperphenylalaninemia (HPA) in adult and pediatric patients one month of age and older with sepiapterin-responsive phenylketonuria (PKU). Sepiapterin is to be used in conjunction with a phenylalanine (Phe)-restricted diet.

POSITION STATEMENT:

Patients with phenylketonuria (PKU) are unable to break down phenylalanine, an amino acid present in protein-containing foods and certain sweeteners used in a variety of foods and beverages. This leads to an accumulation of phenylalanine in the body and if untreated, can manifest as neurocognitive and psychiatric symptoms such as depression, anxiety and intellectual disability. Treatment of PKU is life-long. The American College of Medical Genetics and Genomics guidelines recommend that the goal of treatment is to maintain blood Phe levels between 120 to 360 micromol/L for patients aged 12 years or younger, while levels of up to 600 micromol/L for patients aged 12 years or older. The mainstay of PKU therapy is based around a phenylalanine restricted diet which requires a decrease in the intake of natural protein. This must be supplemented with phenylalanine free, amino acid-based medical foods and beverages. Inadequate compliance to this diet is commonly seen, especially in teenagers and adults. Prior to the approval of pegvaliase (Palynziq) the only medication approved for the treatment of PKU was sapropterin (Kuvan) which is a synthetic analog of tetrahydrobiopterin. Not all patients with PKU will respond to treatment with sapropterin.

The safety and efficacy of pegvaliase was based on two phase 3 trials in adult patients with phenylalanine concentrations greater than 600 micromol/L on existing management. PRISM-1 and PRISM-2. PRISM-1 was an open-label, parallel group phase 3 study in which patients were given an induction, titration, and maintenance dosing regimen of either pegvaliase 20 mg/day or 40 mg/day. The primary outcome of PRISM-1 was focused on safety. The focus of the FDA efficacy review was on PRISM-2 Part 2, which was a randomized discontinuation trial that enrolled patients who were stable on pegvaliase 20 mg/day or 40 mg/day from PRISM-1 who also achieved a blood phenylalanine reduction of at least 20%. The primary end point of this trial was change in blood phenylalanine levels at week eight. The mean change in the patients that remained on pegvaliase was 26.5 µmol/L compared to 949.8µmol/L and 664.8 µmol/L in the 20 mg/day and 40 mg/day placebo groups.

- One advantage of pegvaliase is that, unlike sapropterin, patients do not have to be on a phenylalanine restricted diet.

- Efficacy of pegvaliase in combination with or compared to sapropterin remains unknown as patients were required to discontinue sapropterin use prior to pegvaliase trials. Efficacy and safety of pegvaliase in pediatric patients is also unknown as only patients 18 years and older were included in the clinical trials.
- There are significant safety concerns with pegvaliase including anaphylaxis, which occurred in 9% (n=26) of patients treated with pegvaliase in the clinical trials. Patients are required to be prescribed an auto-injectable epinephrine with pegvaliase and must be enrolled in the Palynziq REMS Program.
- Other adverse effects include arthralgia which was reported in 83% of 285 patients in clinical trials. Nonsteroidal anti-inflammatory drugs, glucocorticosteroids, and/or acetaminophen can be used to manage this adverse effect. Dose reduction to the last tolerated dose can be an alternative approach.

The American College of Medical Genetics and Genomics guidelines for the treatment of PKU were last updated in 2014, prior to the approval of pegvaliase. However, a steering committee of experts in 2019, comprising of health care professionals with experience of pegvaliase use in clinical trials, convened to develop guidance statements to improve long-term outcomes for adults with PKU:

- Goal of treatment with pegvaliase:
    - Provide life-long maintenance of blood Phe levels as low as possible (31 to 120 micromol/L) while normalizing diet (Dietary Reference intake for protein 0.8 gm/kg/day).
- The FDA prescribing information states that pegvaliase should be discontinued in patients who do not achieve an adequate response after 16 weeks of treatment at the **maximum dose of 60 mg once daily.** Therefore, if patient has not met treatment goal and is not at maximum dose of 60 mg daily, may consider up-titration as tolerated. Prescribing information recommends a dose increase to 40 mg daily for those on 20 mg daily for at least 24 weeks without achieving blood PHE control (less than or equal to 600 micromol/L) and an additional dose increase to 60 mg daily if blood PHE control is not reached with at least 16 weeks of treatment on 40 mg daily.
    - In clinical trials, a reduction of 20% or greater at any point within 52 weeks was considered to be first sign of efficacy. Further lowering of blood Phe level may be achieved with continued use.
    - Patients who experienced adverse effects during titration may require a slower titration period. Therefore, an extension of the treatment duration for efficacy assessment should be considered if dose titration took longer or if dose reduction or discontinuation occurred due to adverse effects during titration period.
- Pegvaliase should be considered in adult patients with PKU who are able to give informed consent to treatment.

  - Use with caution in adult patients who may not be able to communicate issues associated with adverse events
  - Patient should have a trained observer accompany the patient for at least one hour after administration for the initial dose and each initial up-titration dose
  - Use with caution in patients with mental health problems or severe anxiety which can impede ability to administer pegvaliase or communicate side effects
- Premedication with H1 and H2 receptor antagonists and antipyretics are recommended prior to initial administration and during titration of pegvaliase.
- **There is currently no data to support the use of pegvaliase and sapropterin in combination.**
- Pegvaliase has not been studied in pregnant women. However, poorly controlled Phe levels during pregnancy can lead to birth defects such as microcephaly, intrauterine fetal growth retardation, and intellectual disability. Women with PKU who are pregnant should maintain rigorous diet management.

The safety and efficacy of sepiapterin was approved based on the Phase 3 APHENITY trial and durability data from the APHENITY open-label extension study.

- APHENITY was a two-part study in adults and pediatric patients with phenylketonuria (PKU and hyperphenylalaninemia (HPA) with at least two blood Phe measurements ≥600 µmol/L. Part 1 tested for responsiveness to Sephience with open-label treatment for 14 days. Patients with a ≥30% reduction in blood phenylalanine (Phe) in Part 1 were considered sepiapterin-responders and randomized (double-blind) to Part 2.
- Concomitant use of sapropterin or pegvaliase was not permitted during the study, and participants were required to complete a 7-day washout period for sapropterin or a 30-day washout period for pegvaliase.
- In APHENITY, after an initial Sephience responder identification and washout period, the trial met its primary endpoint, showing a −64.2% difference in adjusted mean change in blood phenylalanine at Weeks 5 and 6 versus placebo (P <0.0001).

HEALTH EQUITY CONSIDERATIONS

- Newborn screening programs (NBS) to diagnose PKU are not implemented in all countries, which can lead to a delay in diagnosis and undertreatment. Maintenance of blood phenylalanine levels often requires maintaining a phenylalanine restricted diet which carries a high treatment burden due to the importance of adherence, financial and time burdens, social impacts, limited access to dietary management and/or low-protein foods, and limited insurance coverage of low phenylalanine

medical formula. While there are several FDA-approved therapies for the treatment of PKU, they are expensive and often have limited access with strict prior authorization barriers. A US survey showed that higher clinical staffing was associated with high adherence to blood phenylalanine recommendations in certain age groups, however access to specialized health care professionals may be limited in rural locations.

REFERENCE/RESOURCES:

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