COVERAGE AUTHORIZATION GUIDE

PALYNZIQ® (pegvaliase-pqpz) Injection

INDICATION

PALYNZIQ® (pegvaliase-pqpz) is a phenylalanine (Phe)-metabolizing enzyme indicated to reduce blood Phe concentrations in adult patients with phenylketonuria who have uncontrolled blood Phe concentrations greater than 600 micromol/L on existing management.

Important Safety Information
BOXED WARNING: RISK OF ANAPHYLAXIS

- Anaphylaxis has been reported after administration of PALYNZIQ and may occur at any time during treatment with PALYNZIQ

Please see Important Safety Information throughout, including Boxed Warning for risk of anaphylaxis, and full Prescribing Information and Medication Guide.

Palynziq® (pegvaliase-pqpz) Injection

BIOMARIN®

PALYNZIQ REMS

Due to the risk of anaphylaxis (see Boxed Warning and Warnings and Precautions in PALYNZIQ full Prescribing Information), PALYNZIQ is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the PALYNZIQ REMS. Only prescribers, patients, and a limited network of certified pharmacies enrolled in the program are able to prescribe, receive, and dispense PALYNZIQ.

Notable requirements of the PALYNZIQ REMS include the following:

- Prescribers must be certified by enrolling in the program and completing training
- Prescribers must prescribe auto-injectable epinephrine with PALYNZIQ
- Pharmacies must be certified with the program and must dispense only to patients who are authorized to receive PALYNZIQ
- Patients must enroll in the program and be educated about the risk of anaphylaxis by a certified prescriber to ensure they understand the risks and benefits of treatment with PALYNZIQ
- Patients must carry auto-injectable epinephrine with them at all times while taking PALYNZIQ

Further information is available at www.PALYNZIQREMS.com. For information on 340B or for a list of qualified pharmacies, contact PALYNZIQ REMS by telephone at 1-855-758-REMS (1-855-758-7367) Monday thru Friday from 8 AM – 8 PM ET.

"REMS is a safety strategy to manage a known or potential serious risk associated with a medicine and to enable patients to have continued access to such medicines by managing their safe use."

—US Food and Drug Administration

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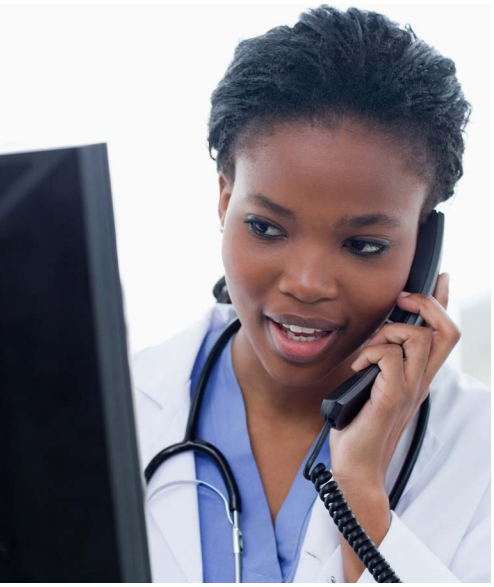
INTRODUCTION AND DISCLAIMER

BioMarin, the manufacturer of PALYNZIQ® (pegvaliase-pqpz) Injection, would like to help every medically appropriate patient with PKU have access to the product. We can help you manage the process of getting your patients on PALYNZIQ. We offer patients and their caregivers assistance through our support services hub, BioMarin RareConnections™, and the BioMarin Clinical Coordinators who also work directly with patients to help educate them on the safe and appropriate use of BioMarin products.

Every patient's insurance plan and health benefits are different, so it is very important to contact each patient's plan for assistance when interpreting drug policies, billing and coding, and payment. These items vary greatly among insurance plans and are subject to change without notice because of frequently changing guidelines, laws, rules, and regulations. Some patients may change insurance plans during the year, so verify current insurance information during each patient visit. If your patient receives a denial, consult the insurance plan to help interpret the denial language, and provide the necessary information and documentation requested by the plan in a timely manner.



Some patients may change insurance plans during the year, so verify current insurance information at each patient visit

Disclaimer

BioMarin has compiled this guide with information gathered from third-party sources and experienced insurance reimbursement experts to assist your practice in obtaining approval and ongoing authorization for PALYNZIQ. While we have included some best practices for working with BioMarin RareConnections, insurance companies, and specialty pharmacies (SPs) in this guide, BioMarin makes no guarantee that the use of this information will prevent denials, delays, or differences of opinion with insurance plans as to the correct information to submit for PALYNZIQ authorization, or forms of billing that will expedite payment to providers of service. BioMarin provides this information as a convenience; it does not constitute legal advice or a recommendation regarding medical practice.

Coding determinations are at the discretion of the provider and should be made in accordance with applicable regulations and payer guidance. Coverage and reimbursement may vary significantly by payer, plan, patient, and setting of care. It is the sole responsibility of the healthcare provider to select the proper codes and ensure the accuracy of all statements used in seeking coverage and reimbursement for an individual patient. Providers should contact third-party payers for specific information on their coding, coverage, and payment policies. Information provided should in no way be considered a guarantee of coverage or reimbursement for any product or service.

This guide covers FDA-approved indications that are documented in the PALYNZIQ full Prescribing Information. Where reimbursement is sought for prescribed use and/or administration of this product that may be inconsistent with, or not expressly specified in, the FDA-cleared or -approved labeling outlined in the PALYNZIQ full Prescribing Information, consult with your billing advisers or insurance plans on handling such issues.

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COORDINATING WITH BIOMARIN RARECONNECTIONS™

BioMarin RareConnections is a resource for patients prescribed PALYNZIQ® (pegvaliase-pqpz) Injection.

BioMarin RareConnections helps patients and healthcare providers navigate the difficulties of managing serious and rare genetic diseases with a wide array of product support services throughout the treatment journey. Our dedicated and experienced Case Managers will provide guidance on how to gain access to PALYNZIQ, including:

- Helping patients understand their insurance coverage and financial assistance options, including the PALYNZIQ Co-Pay Assistance Program for commercially insured, eligible patients*
- Providing ongoing product education and support for PALYNZIQ
- Coordinating with an SP to deliver the patient's medication

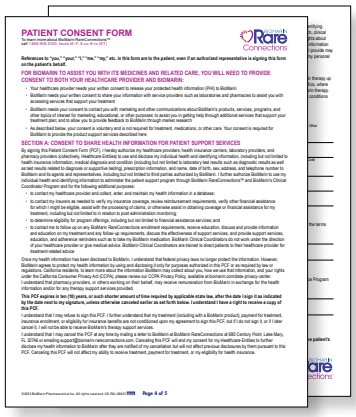
When you are ready to start a patient on PALYNZIQ, contact BioMarin RareConnections at 1-866-906-6100 or email at support@biomarin-rareconnections.com

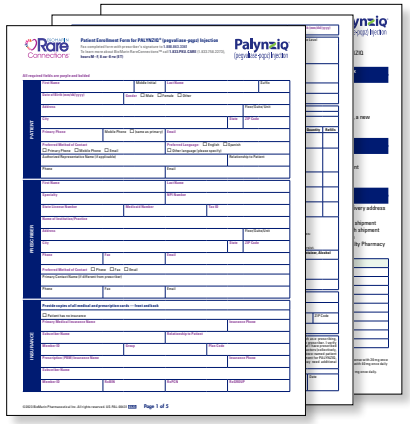
With the PALYNZIQ Co-Pay Assistance Program, 99% of participating patients paid $0 OUT-OF-POCKET for their prescription†

In order to access BioMarin RareConnections product support services, submit both the BioMarin RareConnections Patient Consent Form (PCF) and the Patient Enrollment Form (PEF) and copies of the insurance cards (front and back).

- **PCF:** The Patient Consent Form provides authorization from the patient for the provider/clinic to provide patient-level information to BioMarin and for BioMarin RareConnections to use this patient-level information to communicate with payers and SPs to secure access to the prescribed product
- **PEF:** The Patient Enrollment Form serves as the prescription and provider authorization for BioMarin RareConnections to work on a patient's case

BioMarin RareConnections will contact the healthcare provider's office to confirm receipt of the PEF and PCF and verify the information provided.


PATIENT CONSENT FORM


Patient Enrollment Form for PALYNZIQ® (pegvaliase-pqpz) Injection

*Valid only for those with commercial insurance. Offer not valid for prescriptions eligible to be reimbursed, in whole or in part, by Medicare, Medicaid, or any other federal or state program (including any state prescription drug assistance programs) (e.g., VA, DoD, TriCare), for cash-paying patients, where product is not covered by patient's commercial insurance, or where plan reimburses you for the entire cost of your prescription drug. No claim for reimbursement of the out-of-pocket expense amount covered by the program shall be submitted to any third-party payer, whether public or private. Offer is not valid where prohibited by law. Valid only in the United States and Puerto Rico. This program is not health insurance. Offer may not be combined with any other rebate, coupon, or offer. Co-payment assistance under the program is not transferable. BioMarin Pharmaceutical Inc. reserves the right to rescind, revoke, or amend the program without notice. Patient certifies responsibility for complying with applicable limitations, if any, of any commercial insurance and reporting receipt of program rewards, if necessary, to any commercial insurer. This program is subject to termination or modification at any time.

†Based on 2018 and 2019 co-pay program data. The PALYNZIQ Co-Pay Assistance Program will cover all co-pay costs related to both the PALYNZIQ and auto-injectable epinephrine prescriptions, up to $18,200 in assistance per calendar year for eligible patients, for as long as patient remains on therapy. Eligible patients will receive 3 fills of auto-injectable epinephrine per year at no additional cost. Residents of CA and MA are not eligible for co-pay assistance for auto-injectable epinephrine. Some restrictions apply.

Please see Important Safety Information throughout, including Boxed Warning for risk of anaphylaxis, and full Prescribing Information and Medication Guide.

COORDINATING WITH BIOMARIN RARECONNECTIONS™

BioMarin RareConnections coordinates with the specialty pharmacy

Once BioMarin RareConnections receives all the necessary paperwork, the patient referral is sent to the REMS-certified SP with the prescription (Rx) and patient information for processing and shipment. BioMarin RareConnections and the SP will call your patient to discuss their treatment with PALYNZIQ® (pegvaliase-pqpz) Injection and shipment logistics.

The SP will:

- Verify the Rx and product order
- Verify and collect the patient's out-of-pocket expenses related to PALYNZIQ with each delivery
- Coordinate delivery of PALYNZIQ with the patient and request verbal confirmation of the delivery address prior to sending the medication; the patient or caregiver should be available to accept delivery
- Confirm the patient has an auto-injectable epinephrine pen in their possession that has not expired
- Call the patient to discuss their treatment with PALYNZIQ
- Educate the patient or a caregiver on the special handling and refrigeration requirements for PALYNZIQ to ensure proper storage, care, and disposal of the product
- Coordinate refills with the patient or a caregiver in advance of refill
- Handle replacement product, as needed

Please note the following special instructions:

- SPs will verify REMS clinic certification and patient enrollment prior to each shipment
- Premedication will require a separate prescription if the SP is to ship the premedication
- Auto-injectable epinephrine pen prescription will be needed if the SP is to ship the pen
- SPs will confirm patient need for all selected ancillary supplies prior to each shipment

When you are ready to start a patient on PALYNZIQ, contact BioMarin RareConnections at 1-866-906-6100 or email at support@biomarin-rareconnections.com

BIOMARIN RARECONNECTIONS™ AND SPECIALTY PHARMACY ROADMAP FOR PALYNZIQ® (pegvaliase-pqpz) INJECTION

Patient Enrollment: PCF + PEF

- ✓ HCP notification of PEF receipt
- ✓ Follow-up with HCP on missing information
- ✓ Patient notification of PCF received

Securing Coverage

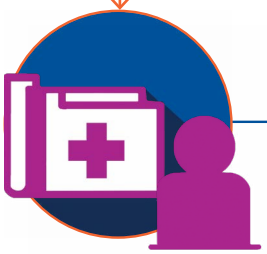
- ✓ Benefits investigation (BI) and prior authorization (PA) requirements assessed
- ✓ Patient welcome call
- ✓ Patient notification of BI results
- ✓ HCP notification of BI results and PA requirements

Financial Assistance Support*

- ✓ Co-Pay Assistance Program eligibility screening
- ✓ BioMarin Patient Assistance Program eligibility screening
- ✓ Referrals to additional support options, if needed

Specialty Pharmacy Triage and Shipment Coordination

- ✓ Verification of prescription and validation of insurance coverage†
- ✓ Shipment coordination with patients
- ✓ Packaging and delivery logistics



Maintaining Therapy‡

- ✓ PA reauthorization
- ✓ Prescription expiration
- ✓ Refill reminders

*As appropriate for eligible patients.

†Specialty pharmacy verifies prescriber is PALYNZIQ REMS (Risk Evaluation and Management Strategy) certified and patient is authorized to receive PALYNZIQ. Before dispensing PALYNZIQ, specialty pharmacy verifies the patient has auto-injectable epinephrine on hand.

‡Specialty pharmacy–dependent processes.

HCP, healthcare provider; PCF, BioMarin RareConnections Patient Consent Form; PEF, BioMarin RareConnections Patient Enrollment Form.

Please see Important Safety Information throughout, including Boxed Warning for risk of anaphylaxis, and full Prescribing Information and Medication Guide.

INSURANCE VERIFICATION AND WORKING WITH BIOMARIN RARECONNECTIONS™

Does your patient have insurance coverage for PALYNZIQ® (pegvaliase-pqpz) Injection treatment?

Now that you and your patient have decided to use PALYNZIQ to treat your patient's PKU, it is important to understand how to gain access to the treatment. PALYNZIQ is a self-administered at-home subcutaneous injection and is a specialty treatment. Managing and accessing a specialty drug is quite different from a typical prescription filled at a local retail pharmacy. Understanding if and how your patient's insurance covers PALYNZIQ is the first step, and BioMarin has included some suggestions below to help you.

Completing the prior authorization requirements

1 

Before a patient can be treated with PALYNZIQ, the patient's insurance benefits should be verified

2 

Make copies of the medical and pharmacy benefit insurance cards, and upload the insurance information to your patient's medical record

3 

Always ask at each office visit if there have been changes to the patient's insurance

BioMarin RareConnections provides support every step of the way, including:

Verify the patient's insurance benefits

- Contacting the insurance plan to inquire about the patient's access to PALYNZIQ, ie, insurance benefits/coverage for PALYNZIQ, including any prior authorization (PA) requirements that your clinic will need to submit to secure insurance coverage for the patient
- Reviewing the information you provide to support the PA request, and contacting your clinic to gather any missing information or additional details that the insurance plan may require to complete the PA
- Assisting with the submission of the PA (prepared by the clinic) to the patient's insurance plan, if you desire, and supporting your clinic with PA denials/appeals, if applicable
- Contacting the patient to discuss any associated out-of-pocket expenses (e.g., deductible, co-payments, coinsurance) for PALYNZIQ; however, the SP will collect the co-payment with each delivery
- If your patients have financial concerns about affording the product, they should speak with BioMarin RareConnections to find out if there are any options available to help
- Managing any additional questions that arise

Additionally, BioMarin RareConnections PKU Field Reimbursement Managers (FRMs) can work directly with you to share best practices for managing the PALYNZIQ prescription fulfillment process. They can also provide insight on the patient's insurance plan, education on the access and reimbursement process, a checklist for PA requirements provided by the plan, and support with the appeals process. The PKU FRM works in coordination with the patient's BioMarin RareConnections Case Manager and is your 1:1 informational resource for clinics to assist with:

- Individualized reimbursement support for patients, including coordinated communication with BioMarin RareConnections Case Managers and facilitation of cases/situations as needed
- BioMarin RareConnections overview (program services and tools, co-pay program, website)
- General reimbursement education (PA appeal support, regional payer insights/trends, formulary changes)
- SP education and support

Please see Important Safety Information throughout, including Boxed Warning for risk of anaphylaxis, and full Prescribing Information and Medication Guide.

TREATMENT AUTHORIZATION AND REAUTHORIZATION

Prescribing PALYNZIQ® (pegvaliase-pqpz) Injection

PALYNZIQ is a specialty drug. Specialty drugs often require additional verification steps from the patient's insurance plan. The insurance plan manages access to specialty drugs because they want to ensure the drugs are used in the appropriate patient population.

After BioMarin RareConnections™ verifies the patient's insurance benefits, your clinic may be required to complete a PA request from the insurance plan. Timing of PA submissions is important and varies by plan. The insurance plan will review the completed PA and supporting medical documentation, and then provide a determination. A determination is either an approval or denial for the specialty drug, usually obtained within 24 to 72 hours.

PALYNZIQ has a minimum recommended induction and titration phase to achieve effective maintenance dosage and is available in different dosage strengths. During the titration phase, insurance plans may require additional PA requests for each increase or reduction in dose, titration success, clinical response when optimizing the maintenance dosage, and/or adherence to therapy. Plans may also choose to have the SP call to confirm the next increasing dose, or request recent lab results and medical documentation indicating how the patient is progressing on PALYNZIQ. It would be helpful for your clinic to assign 1 or more individuals to manage your patient access support, so forms are processed quickly and do not get lost. It will be very important to monitor the phone, fax, email, and/or mail for any communication from the patient's insurance plan or SP for every patient who is prescribed PALYNZIQ. Insurance plans may expect monitoring and oversight of these patients by their prescribing physicians.

A prior authorization, or PA, is a request for authorization and coverage of PALYNZIQ by the insurance plan. It is usually a 1- to 2-page form that asks questions to confirm diagnosis, supporting medical documentation, treatment history, and a written statement from the prescriber stating why PALYNZIQ is the proper treatment for the patient.

We have provided an example letter for your reference when drafting a letter of medical necessity for each patient case. When completing the PA package, it's a good idea to include any relevant personal details about the patient based on your clinical assessment and his or her unique treatment journey. Be as descriptive as you can about the patient's personal burden of illness and diet and disease management struggles. Including specific examples of the patient's personal treatment journey and your medical opinion of the need for treatment with PALYNZIQ will provide important context for the payer. Be sure to include the required supporting medical documentation as part of the PA package.

Requesting prior authorization for PALYNZIQ

- Write a letter of medical necessity
- Complete and submit the PA paperwork, supporting medical documentation, and letter of medical necessity to the insurance plan's contact, information for which is listed on the PA form
- If the insurance plan requests additional documentation, provide it in a timely manner

By requesting multiple dose strengths on the initial PA, if allowed, a new PA may not be required for titrating to a different dose. See page 25.

- Monitor for any communication from the patient's insurance plan
- If you utilize BioMarin RareConnections™, they will be able to help monitor approvals and denials. Denials may also be communicated by a letter mailed to the patient and the clinic
- BioMarin RareConnections is available to assist clinics with PA denials and appeals, if applicable

When completing the PA, please highlight laboratory tests and results pertinent to blood phenylalanine levels with any prior treatment, including but not limited to any history of response to sapropterin dihydrochloride.

Examples of supporting medical documentation

- For initiation of treatment
  - ICD-10-CM codes pertinent to the diagnosis of PKU
  - Patient medical history or consultation report(s) discussing the patient's diagnosis and medical necessity for treatment with PALYNZIQ® (pegvaliase-pqpz) Injection
  - Laboratory tests and results pertinent to baseline or uncontrolled blood Phe levels
  - Treatment history
  - Diet records or notes by a dietitian documenting patient's history of diet monitoring and adherence
  - Healthcare provider chart notes
- For titration and maintenance stages
  - Documented patient tolerability during titration phase (adverse events on a lower dose may lead to denials for higher doses)
  - Recent lab results showing current Phe levels since therapy initiation
  - Monitored dietary protein and phenylalanine intake
  - If the decision is made to titrate to the maximum maintenance dose of 60 mg:
    - Clearly document need for the 60 mg dose (3 daily injections of 20 mg) supported by the PALYNZIQ Prescribing Information
    - Include documentation of any nonresponse at the 40 mg dose and criteria considered when escalating to 60 mg
    - Provide any dietary documentation or records related to the patient's treatment plan
- Other examples of supporting documentation
  - Any shared decision-making notes from multidisciplinary discussions or case conferences

Some plans may require an override when therapy exceeds a certain quantity or cost. See page 25.

Examples of patient's treatment history

- Phe-restricted diet treatment history
- KUVAN® (sapropterin dihydrochloride) Tablets or Powder for Oral Use treatment history: KUVAN nonresponder, KUVAN discontinued, KUVAN-naïve
- Previous PALYNZIQ clinical trial patient, moving from trial to commercial drug
- Current PALYNZIQ patient, requiring a dose change during titration phase

Please see Prior Authorization Checklist on page 11.

If your patient just switched to a higher dose (e.g., 60 mg) during the reauthorization window and has not achieved the required Phe reduction from baseline, please request reauthorization based on the titration regimen per the PALYNZIQ® (pegvaliase-pqpz) Injection Prescribing Information while reiterating the necessity of the higher dose.

Reauthorization

Insurance plans typically authorize treatment for 1 year, so each year they may require the prescriber to issue a new prescription and reauthorize treatment with PALYNZIQ. The patient's insurance plan may request data to demonstrate any changes in Phe levels from baseline and have assurance that patients adhere to dietary restrictions when being treated with PALYNZIQ. BioMarin encourages prescribers to provide any dietary documentation or records related to the patient's treatment plan.

BioMarin RareConnections™ and SPs also provide the following services for patients who are receiving their drug through the SP channel:

- Informing the patient and the prescriber if treatment reauthorization is required by the patient's health insurance
- Requesting prescribers to submit an updated prescription with any additional information to include in the reauthorization
- Informing the patient and the prescriber if treatment is reauthorized for another year, or if the insurance plan requires additional information

A dosage change may require submitting a new PA. See page 25.

PRIOR AUTHORIZATION/ REAUTHORIZATION CHECKLIST

Checklist for a prior authorization for PALYNZIQ

Utilize the following checklist to ensure that all relevant information is captured before submitting a PA for PALYNZIQ. All services must be medically appropriate and properly supported in the patient's medical record based on determination by the prescriber. A letter of medical necessity should accompany all submitted information.

The following items may be requested by the patient's insurance plan for inclusion in the PA/medical necessity request:

Key PA criteria* (information usually requested by insurance plans)

- ☐ ICD-10-CM diagnosis and description
- ☐ Patient age
- ☐ Blood Phe concentration prior to treatment

Additional information required, depending on specific health plan or providers

- ☐ Supporting medical documentation: medical history, clinical notes, medication records, and relevant lab results. Most recent clinical notes or last 6 months for PA renewals or reauthorizations
- ☐ Phe levels: current Phe levels (treatment history compared to baseline). Initial PA: baseline Phe levels. Renewal PA: current Phe levels compared to baseline.
- ☐ Treatment history
- ☐ Response to prior treatment: documentation of therapeutic failure or intolerance to existing management
- ☐ Dietitian's notes or records documenting careful diet monitoring and adherence
- ☐ REMS forms

Payer restrictions can take a variety of forms and will apply both to initial authorization and reauthorizations. Payers may have dietary restrictions in place that are not required by the current PALYNZIQ Prescribing Information so additional documentation regarding diet monitoring may be required.

*Individual plan requirements may vary.

SAMPLE LETTER OF MEDICAL NECESSITY FOR PALYNZIQ® (pegvaliase-pqpz) INJECTION TREATMENT

- ✔ Date
- ✔ Patient Name
- ✔ Patient Mailing Address
- ✔ Patient Contact Phone Number
- ✔ Insurance Plan Name
- ✔ Insurance Plan Mailing Address
- ✔ Insurance Subscriber Name
- ✔ Insurance Subscriber ID Number
- ✔ Effective Date of Coverage

RE: Authorization of PALYNZIQ® (pegvaliase-pqpz) Injection Treatment

Dear Sir or Madam:

I am writing on behalf of my patient, [insert patient name], to request approved authorization and coverage from [insert insurance plan name] for PALYNZIQ. My patient has been diagnosed with phenylketonuria (PKU), also referred to as "phenylalanine hydroxylase deficiency" (PAHD). PKU is a rare, inherited, lifelong metabolic disorder. Adult patients with PKU, unless managed, have elevated blood phenylalanine (Phe) concentrations that are neurotoxic and they may experience serious neurologic, psychiatric, and psychological complications and comorbid conditions across multiple organ systems. The American College of Medical Genetics and Genomics (ACMG) published practice guidelines recommend that treatment should be lifelong, with treated blood Phe levels in the range of 120 to 360 µmol/L for all patients of all ages, and that a reduction in blood Phe levels, increase in dietary Phe tolerance, and improvement in clinical symptoms are all valid indications for continuation of therapy.

PALYNZIQ is a phenylalanine-metabolizing enzyme indicated to reduce blood phenylalanine in adult patients with phenylketonuria who have uncontrolled blood phenylalanine levels >600 µmol/L on existing management. This letter provides information about my patient's medical and treatment history, diagnosis, and details regarding the medical necessity for treatment with PALYNZIQ.

Patient's medical history

My patient's current disease state, prior treatment, and response to those treatments, as well as other issues that influence my treatment decision are:

- ✔ *Insert brief description of patient: age, functional status, PKU history, and prior treatment history*
- ✔ *Include essential lab results and genetic testing history that verify PKU diagnosis and demonstrate uncontrolled Phe levels*
- ✔ *Include other factors that impact the treatment decision (e.g., comorbidities, work status, etc)*
- ✔ *Include supporting medical documentation and notes to support the patient's case*
- ✔ *If patient has previously tried KUVAN® (sapropterin dihydrochloride), it is helpful to include that information; indicate treatment failure or nonresponsiveness to sapropterin/KUVAN, or inability to control blood Phe with sapropterin plus diet as recommended by clinical guidelines or individual treatment goals*
- ✔ *Patient's history with diet/formula*

Disease and treatment information

I have attached the prescribing information for PALYNZIQ, which was approved by the US Food and Drug Administration (FDA) on May 24, 2018.

PALYNZIQ is an injectable at-home treatment for PKU intended for self-administration once daily with a rigorous 9-week recommended induction and titration period leading to maintenance dosing. I am requesting a 1-year approval for all dosages that my patient will require during the induction, titration, and maintenance phases to reach the maintenance dose of PALYNZIQ and achieve blood Phe control. PALYNZIQ is supplied in the following forms: 2.5 mg/0.5 mL single-dose prefilled syringes, 10 mg/0.5 mL single-dose prefilled syringes, and 20 mg/1 mL single-dose prefilled syringes. Providing approval for all doses will ensure that my patient will be able to successfully manage the recommended dosing regimen, thus reaching the effective therapeutic dose with no interruption or delay.

SAMPLE LETTER OF MEDICAL NECESSITY FOR PALYNZIQ® (pegvaliase-pqpz) INJECTION TREATMENT (continued)

Recommended dosing regimen		
TREATMENT	**PALYNZIQ DOSAGE**	**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 per week	1 week
	10 mg once daily	1 week
Maintenance†	20 mg once daily	24 weeks
	40 mg once daily	16 weeks
Maximum‡	60 mg once daily	16 weeks

*Additional time may be required prior to each dosage escalation based on patient tolerability.

†Individualize treatment to the lowest effective and tolerated dosage. Consider increasing to 40 mg once daily in patients who have not achieved a response with 20 mg once daily continuous treatment for at least 24 weeks. Consider increasing to a maximum of 60 mg once daily in patients who have not achieved a response with 40 mg once daily continuous treatment for at least 16 weeks *(see Clinical Studies [14] section of Prescribing Information).*

‡Discontinue PALYNZIQ in patients who have not achieved an adequate response after 16 weeks of continuous treatment at the maximum dosage of 60 mg once daily.

In conclusion, I am requesting that you approve treatment for my patient, [insert patient name], with PALYNZIQ. Please contact me with any additional questions or if you require additional information.

Sincerely,

[Insert prescriber name,
credentials, contact information]

SUGGESTED ENCLOSURES

- PALYNZIQ Patient Prescription or Patient Enrollment Form
- PALYNZIQ Prescribing Information
- PALYNZIQ published clinical studies
- Patient medical history, clinical notes, and lab results confirming diagnosis
- Relevant lab results: e.g., genetic tests, Phe levels reflective of patient's current diet status and lifestyle

Please see Important Safety Information throughout, including Boxed Warning for risk of anaphylaxis, and full Prescribing Information and Medication Guide.

MANAGING DENIALS AND APPEALS

Denials occur when the insurance plan does not have enough information to confirm that a patient is the right candidate for a specialty treatment. They can also occur if the patient does not meet the clinical criteria for approval, as specified by the insurance plan. Specialty drugs are often denied following an initial authorization request, and changing the denial will require writing an appeal or conducting a peer-to-peer discussion. The insurance plan will provide a written rationale for the denial to both prescriber and patient, usually by mail. Read these letters carefully, as they will provide the reasons for denial, methods for appealing the denial, and time frame to request an appeal. If you do not understand the denial letter, contact the patient's insurance plan to request additional information. Please provide a copy of the denial letter to the BioMarin RareConnections™ for further assistance.

When completing a PA Appeal, be sure to include the required missing documentation and refer to the example PA Appeal letter. Provide any relevant details about the patient's personal burden of illness and diet and disease management struggles. Including specific and personal details about the patient's unique treatment journey and your medical opinion of his or her need for treatment with PALYNZIQ® (pegvaliase-pqpz) Injection will provide important context for the payer.

Additional insurance plan requests

The denial letter may include requests for additional medical information, including medical records, laboratory work, genetic testing records, and/or the healthcare provider's medical rationale for selecting PALYNZIQ as medically necessary for his/her patient.

Evaluate the methods for appealing in the letter or contact the insurance plan directly to understand your appeal options. Often written appeals are the first option provided, but if a **peer-to-peer discussion** is available, this is the preferred and most expeditious means of appealing a denial.

Three types of appeals

1 

Peer-to-peer discussion: A peer-to-peer appeal is a phone call where the prescriber can verbally provide the missing data for the insurance plan and explain his/her rationale for selecting a particular treatment. Adjudication for coverage could be provided during the call or be issued in a letter format.

2 

Appeal letter: A formal, written letter is the usual and customary first level of appeal. This letter is the first attempt to answer or provide additional information requested by the insurance plan. Adjudication for coverage will be returned in letter format.

Peer-to-peer appeals are the preferred and most expeditious means of appealing a denial.

3 

External review: If the insurance plan denies authorization for treatment multiple times, patients can appeal to an external court or administrative law judge for review of treatment authorization. The letter must be written by the patient, and if an in-person meeting is granted, it must be conducted by the patient or the patient's legal representative. The prescriber may also attend to provide additional detail to support the appeal. Policies and specifics for this level of denial are state-specific, and it is recommended that patients or caregivers seek legal advice.

Every insurance plan is different; remember to read the denial carefully and identify the appeal timelines.

Please see Important Safety Information throughout, including Boxed Warning for risk of anaphylaxis, and full Prescribing Information and Medication Guide.

SAMPLE APPEAL LETTER FOR PALYNZIQ® (pegvaliase-pqpz) INJECTION TREATMENT

- ✔ Date
- ✔ Patient Name
- ✔ Patient Mailing Address
- ✔ Patient Contact Phone Number
- ✔ Insurance Plan Name
- ✔ Insurance Plan Mailing Address
- ✔ Insurance Subscriber Name
- ✔ Insurance Subscriber ID Number
- ✔ Effective Date of Coverage

RE: Appeal letter for denied authorization for PALYNZIQ® (pegvaliase-pqpz) Injection

Dear Sir or Madam:

I am writing on behalf of my patient, [insert patient name], to appeal the [insert date] denial for coverage of PALYNZIQ. My patient has phenylketonuria (PKU), also referred to as "phenylalanine hydroxylase deficiency" (PAHD). This letter provides the additional information requested by [insert insurance plan name] in the denial letter and is a formal request for appeal and expedited review of my request for PALYNZIQ coverage for [insert patient name].

Disease and treatment information

PALYNZIQ is a phenylalanine-metabolizing enzyme indicated to reduce blood phenylalanine in adult patients with phenylketonuria who have uncontrolled blood phenylalanine levels >600 µmol/L on existing management. This appeal letter provides additional information about my patient's medical and treatment history, diagnosis, and details regarding the medical necessity for treatment with PALYNZIQ. PALYNZIQ was approved by the US Food and Drug Administration (FDA) on May 24, 2018.

PKU is a rare, inherited, lifelong metabolic disorder. Adult patients with PKU, unless managed, have elevated blood phenylalanine (Phe) concentrations that are neurotoxic and they may experience serious neurologic, psychiatric, and psychological complications and comorbid conditions across multiple organ systems. The American College of Medical Genetics and Genomics (ACMG) published practice guidelines recommend that treatment should be lifelong, with treated blood Phe levels in the range of 120 to 360 µmol/L for all patients of all ages, and that a reduction in blood Phe levels, increase in dietary Phe tolerance, and improvement in clinical symptoms are all valid indications for continuation of therapy.

I am requesting that you reassess the denial decision in light of the additional information I have provided and that you please approve my request for PALYNZIQ treatment for [insert patient name].

Patient's medical history

My patient's current disease state, prior treatment, and response to those treatments, as well as other issues that influence my treatment decision are:

- ✔ *Insert brief description of patient: age, functional status, PKU history, and treatment history*
- ✔ *Include any additional lab results and genetic testing history that verify PKU diagnosis and demonstrate uncontrolled Phe levels that were not included with the original letter of medical necessity, e.g., neurocognitive or neuropsychiatric tests*
- ✔ *Include any additional supporting medical documentation (e.g., relevant excerpts from patient medical records, clinical notes, medication records, relevant lab results, etc) that were not included with the original letter of medical necessity; include notes to support the patient's case*
- ✔ *Provide compelling medical rationale for selecting PALYNZIQ as medically necessary treatment for your patient*
- ✔ *If patient has previously tried KUVAN® (sapropterin dihydrochloride), it is helpful to include that information; indicate treatment failure or nonresponsiveness to sapropterin/KUVAN, or inability to control blood Phe with sapropterin plus diet as recommended by clinical guidelines or individual treatment goals*
- ✔ *Patient's history with diet/formula*

SAMPLE APPEAL LETTER FOR PALYNZIQ® (pegvaliase-pqpz) INJECTION TREATMENT (continued)

In conclusion, I am asking [insert insurance plan name] to reconsider your decision to deny my patient access to PALYNZIQ® (pegvaliase-pqpz) Injection. I request that [insert insurance plan name] issue a 1-year approval for all dosages my patient will require to reach the maintenance dose of PALYNZIQ and achieve blood phenylalanine control.

Sincerely,

[Insert prescriber name,
credentials, contact information]

SUGGESTED ENCLOSURES

- Copy of denial letter
- PALYNZIQ Patient Prescription or Patient Enrollment Form
- PALYNZIQ Prescribing Information
- PALYNZIQ published clinical studies
- Patient medical history, clinical notes, and lab results confirming diagnosis
- Relevant lab results: e.g., genetic tests, Phe levels reflective of patient's current diet status and lifestyle
- If prescribing a dosing regimen other than the recommended dosing regimen outlined in the PALYNZIQ Prescribing Information, please provide an explanation

SAMPLE APPEAL LETTER FOR PALYNZIQ® (pegvaliase-pqpz) INJECTION TREATMENT FOR PLANS WITH COVERAGE EXCLUSIONS

- ✔ Date
- ✔ Patient Name
- ✔ Patient Mailing Address
- ✔ Patient Contact Phone Number
- ✔ Insurance Plan Name
- ✔ Insurance Plan Mailing Address
- ✔ Insurance Subscriber Name
- ✔ Insurance Subscriber ID Number
- ✔ Effective Date of Coverage

RE: Appeal letter requesting a 1-year authorization exception for PALYNZIQ® (pegvaliase-pqpz) Injection for patients on previously approved PALYNZIQ therapy

Dear Sir or Madam:

I am writing on behalf of my patient, [insert patient name], to request that you authorize continued coverage for their current therapy on PALYNZIQ. PALYNZIQ is a phenylalanine-metabolizing enzyme substitution therapy indicated to reduce blood phenylalanine in adult patients with phenylketonuria who have uncontrolled blood phenylalanine levels >600 µmol/L on existing management. PALYNZIQ can metabolize blood Phe irrespective of residual PAH enzyme activity and could therefore theoretically work in any PKU patient.

My patient has phenylketonuria (PKU), which is a rare, inherited, lifelong metabolic disorder. Adult patients with PKU, unless managed, have elevated blood phenylalanine (Phe) concentrations that are neurotoxic, and they may experience serious neurologic, psychiatric, and psychological complications and comorbid conditions across multiple organ systems. The American College of Medical Genetics and Genomics (ACMG) published practice guidelines recommending that treatment should be lifelong, with treated blood Phe levels in the range of 120 to 360 µmol/L for all patients of all ages, and that a reduction in blood Phe levels, increase in dietary Phe tolerance, and improvement in clinical symptoms are all valid indications for continuation of therapy.

Patient's medical history

My patient's current disease state, prior treatment, and response to those treatments, as well as other issues that influence my treatment decision are:

- ✔ *Insert brief description of patient: age, functional status, PKU history, and treatment history*
- ✔ *Include any additional lab results and genetic testing history that verify PKU diagnosis and demonstrate uncontrolled Phe levels that were not included with the original letter of medical necessity, e.g., neurocognitive or neuropsychiatric tests*
- ✔ *Include any additional supporting medical documentation (e.g., relevant excerpts from patient medical records, clinical notes, medication records, relevant lab results, etc.) that were not included with the original letter of medical necessity; include notes to support the patient's case*
- ✔ *Provide compelling medical rationale for selecting PALYNZIQ as medically necessary treatment for your patient, including if they are receiving clinically meaningful benefit on therapy*
- ✔ *If patient has previously tried KUVAN® (sapropterin dihydrochloride), it is helpful to include that information; indicate whether patient was a sapropterin responder, if they did not have a clinically meaningful therapeutic response to sapropterin and/or that there was an inability to control blood Phe with sapropterin plus diet as recommended by clinical guidelines or individual treatment goals, if relevant*
- ✔ *Include patient's history with diet/formula*

SAMPLE APPEAL LETTER FOR PALYNZIQ® (pegvaliase-pqpz) INJECTION TREATMENT FOR PLANS WITH COVERAGE EXCLUSIONS (continued)

I am requesting a 1-year exception for my patient to continue on their previously approved PALYNZIQ therapy. This exception should apply for all dosages that my patient may require during any phase of treatment, including the induction, titration, and maintenance phases to reach the maintenance dose of PALYNZIQ to achieve blood Phe control. PALYNZIQ is supplied in the following forms: 2.5 mg/0.5 mL single-dose prefilled syringes, 10 mg/0.5 mL single-dose prefilled syringes, and 20 mg/1 mL single-dose prefilled syringes. Providing approval for all doses will ensure that my patient will be able to successfully manage the recommended dosing regimen as prescribed, thus giving the patient the best opportunity to reach an effective therapeutic dose with no interruption or delay.

Sincerely,

[Insert prescriber name,
credentials, contact information]

SUGGESTED ENCLOSURES

- Copy of denial letter
- PALYNZIQ Patient Prescription or Patient Enrollment Form
- PALYNZIQ Prescribing Information
- PALYNZIQ published clinical studies
- Patient medical history, clinical notes, and lab results confirming diagnosis
- Relevant lab results: e.g., genetic tests and Phe levels reflective of patient's current diet status and lifestyle
- If prescribing a dosing regimen other than the recommended dosing regimen outlined in the PALYNZIQ Prescribing Information, please provide that information

FINANCIAL ASSISTANCE SUPPORT

Financial assistance

BioMarin Co-Pay Assistance Program: BioMarin RareConnections™ can help commercially insured patients determine eligibility for the PALYNZIQ® (pegvaliase-pqpz) Injection Co-Pay Assistance Program.* The program helps cover 100% of co-pay costs, up to the patient's annual maximum benefit, for eligible patients. The PALYNZIQ Co-Pay Assistance Program is for commercially insured patients only, and certain terms and conditions may apply.

BioMarin Bridge Program

The Bridge Program provides free product on a temporary basis to patients experiencing a coverage or insurance delay for authorization of PALYNZIQ treatment. BioMarin RareConnections can monitor the patient's PA, and if a delay occurs, will reach out to the HCP to discuss writing a Bridge prescription. The Bridge Program has certain eligibility rules and limitations to the amount of Bridge product provided, and BioMarin RareConnections will discuss these directly with the patient and provider. BioMarin Bridge product will be delivered by BioMarin's free drug SP.

BioMarin Patient Assistance Program

The BioMarin Patient Assistance Program (PAP) provides free product to eligible patients who are uninsured or functionally uninsured. BioMarin RareConnections will work with the patient and provider to discuss eligibility. A PAP application and attestation must be completed by the patient and HCP, the patient must meet certain eligibility requirements as outlined by BioMarin, and the product will be delivered by BioMarin's free drug SP. Patients eligible for the PAP are approved for the remainder of the current calendar year unless their insurance coverage changes.

Requesting a cost tier exception may benefit patients who find PALYNZIQ cost-prohibitive. See page 25.

With the PALYNZIQ Co-Pay Assistance Program, 99% of participating patients paid $0 OUT-OF-POCKET for their prescription†

*Valid only for those with commercial insurance. Offer not valid for prescriptions eligible to be reimbursed, in whole or in part, by Medicare, Medicaid, or any other federal or state program (including any state prescription drug assistance programs) (e.g., VA, DoD, TriCare), for cash-paying patients, where product is not covered by patient's commercial insurance, or where plan reimburses you for entire cost of your prescription drug. No claim for reimbursement of the out-of-pocket expense amount covered by the program shall be submitted to any third-party payer, whether public or private. Offer is not valid where prohibited by law. Valid only in the United States and Puerto Rico. This program is not health insurance. Offer may not be combined with any other rebate, coupon, or offer. Co-payment assistance under the program is not transferable. BioMarin Pharmaceutical Inc. reserves the right to rescind, revoke, or amend the program without notice. Patient certifies responsibility for complying with applicable limitations, if any, of any commercial insurance and reporting receipt of program rewards, if necessary, to any commercial insurer. This program is subject to termination or modification at any time.

†Based on 2018 and 2019 co-pay program data. The PALYNZIQ Co-Pay Assistance Program will cover all co-pay costs related to both the PALYNZIQ and auto-injectable epinephrine prescriptions, up to $18,200 in assistance per calendar year for eligible patients, for as long as patient remains on therapy. Eligible patients will receive 3 fills of auto-injectable epinephrine per year at no additional cost. Residents of CA and MA are not eligible for co-pay assistance for auto-injectable epinephrine. Some restrictions apply.

Please see Important Safety Information throughout, including Boxed Warning for risk of anaphylaxis, and full Prescribing Information and Medication Guide.

SPECIALTY PHARMACY SHIPMENT COORDINATION

Once the patient's PA is approved and the financial elements are taken care of, PALYNZIQ® (pegvaliase-pqpz) Injection is delivered by the SP directly to the patient's home. BioMarin is contracted with a limited distribution network of SPs to distribute PALYNZIQ. The SPs coordinate shipment and logistics for ongoing refill management of PALYNZIQ and can also provide case management on PALYNZIQ PA renewals, prescription changes, and dose modifications.

There are a few key aspects on the coordination of the SP shipment that are important to consider:

PALYNZIQ SP distribution facts

- SPs are licensed and REMS certified to dispense PALYNZIQ in all 50 states
- PALYNZIQ is not sold or distributed via wholesalers to individual clinics or in-clinic pharmacy sites. It is currently only available via the 4 REMS-certified SPs. A clinic can only access these SPs by working through BioMarin RareConnections™
- SPs can ship medication to the patient's home or to the clinic
  - Directly to the patients' home
    - Patient will be required to bring the first dose of medication and auto-injectable epinephrine pen to their first appointment at the clinic (also known as "brown bagging")
    - There may be a signature requirement upon delivery when deemed necessary by the patient's insurance plan, due to high theft zones or inclement weather conditions
  - Directly to a healthcare clinic (in patient's name), where requested and permitted by the clinic
    - The SP will need to confirm clinic shipping address, medication strength and quantity, and clinic appointment date
    - The healthcare clinic will need to ensure there is a staff member available to sign for the delivery
    - The SP can ship up to the first 30 days' supply to the clinic
    - The healthcare clinic can remove the first syringe for onsite training and send the rest of the medication home with the patient

Consider having PALYNZIQ shipped to the pharmacy if it cannot be shipped to the clinic or if home delivery is inconvenient for the patient.

REMINDER: PALYNZIQ can be safely stored in the original carton at room temperature for up to 30 days. Do not re-refrigerate once stored at room temperature.

- Auto-injectable epinephrine
  - Patient possession of auto-injectable epinephrine is a REMS requirement. SP confirmation that patient has unexpired auto-injectable epinephrine in their possession expired prior to each shipment is also a REMS requirement
    - Patients should be encouraged to answer calls from the SP confirming delivery and their possession of an unexpired epinephrine pen
  - There are 2 options for patients to obtain auto-injectable epinephrine:
    1. Retail pharmacy: If the patient chooses to obtain the auto-injectable epinephrine at a local retail pharmacy, the healthcare clinic will need to provide the patient with a separate prescription that can be filled at a local retail pharmacy

Please see Important Safety Information throughout, including Boxed Warning for risk of anaphylaxis, and full Prescribing Information and Medication Guide.

2. Specialty pharmacy: If the clinic would like the SP to ship the auto-injectable epinephrine along with PALYNZIQ® (pegvaliase-pqpz) Injection, the prescription may be sent to BioMarin RareConnections™ at the same time the Patient Enrollment Form (PEF) is submitted, or may be submitted directly to the servicing SP

– BioMarin RareConnections will bundle the information and send it to the in-network SP specified by the patient's insurance plan

- Premedication

– There are 2 options for patients to obtain premedications

1. Retail pharmacy:
   - The patient may choose to pick up their premedication over the counter at their local pharmacy
2. Specialty pharmacy:
   - The SP may ship premedication depending on the patient's insurance plan
   - Additional authorization may be needed for the SP to ship nonspecialty drug(s). The servicing SP will work with your clinic to coordinate as needed.
   - If the clinic or patient would like the SP to ship patient's prescribed premedication along with PALYNZIQ, the prescription for the premedication may be sent to BioMarin RareConnections at the same time the Patient Enrollment Form (PEF) is submitted, or may be submitted directly to the servicing SP

Should the patient require a sharps container or other ancillary supplies, please specify the items on the PEF. The SP will reach out to the patient to coordinate the shipment and confirm if additional ancillary supplies/sharps containers are needed.

To start a patient on PALYNZIQ, the prescriber will need to email/fax the completed PCF/PEF with the prescriber's signature and/or any related prescriptions that the patient wants filled by the SP to BioMarin RareConnections at:

Fax: 1-888-863-3361

Email: support@biomarin-rareconnections.com

Phone: 1-833-PKU-CARE (1-833-758-2273), M–F, 8 AM–8 PM ET

BioMarin RareConnections will perform a benefits investigation and provide the clinic with information on insurance plan–specific requirements for PAs, if required. BioMarin RareConnections™ will identify the payer-preferred SP and the case will be triaged to the servicing in-network SP per the patient's plan.

Once the SP has the referral, it will perform the following validations:

- Review the PALYNZIQ prescription
- Confirm the prescriber is REMS certified and patient is REMS enrolled
- Confirm that they (the SP) can service the patient (per the patient's plan)
- Confirm the patient has coverage for product
- Confirm that the patient has possession of their prescribed unexpired auto-injectable epinephrine

The SP may reach out to both the patient and healthcare clinic for anything that needs clarification related to the prescriptions they are filling.

Please see Important Safety Information throughout, including Boxed Warning for risk of anaphylaxis, and full Prescribing Information and Medication Guide.

CODING

Possible coding for managing PALYNZIQ® (pegvaliase-pqpz) Injection dosing, titration, and monitoring

The following coding examples are provided by BioMarin but are not considered a guarantee for reimbursement.

PALYNZIQ

Code Type	Code(s)	Descriptors
ICD-10 Diagnosis Code	E70.0	Classical phenylketonuria (PKU)
	E70.1	Other hyperphenylalaninemias
PALYNZIQ National Drug Codes	68135-0058-90	1 x 2.5 mg carton
	68135-0756-20	1 x 10 mg carton
	68135-0673-40	1 x 20 mg carton
	68135-0673-45	10 x 20 mg carton

PALYNZIQ is a self-administered injectable drug; however, initial administration(s) will be performed under the supervision of a healthcare provider until patient competency with self-administration has been confirmed. Some insurance plans may allow healthcare providers to bill for training of the patient; contact the patient's insurance plan to discuss coding options.

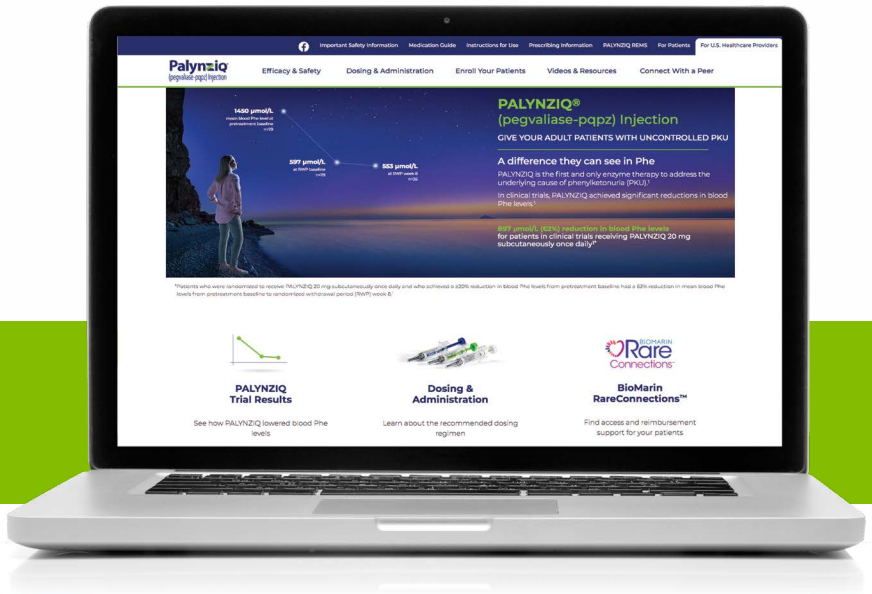
ADDITIONAL INFORMATION AND RESOURCES

PALYNZIQ® (pegvaliase-pqpz) Injection. For additional information about PALYNZIQ resources, visit the product website at PALYNZIQ.com/hcp to find the following:

- All needed paperwork to enroll your patients to start PALYNZIQ therapy
- PALYNZIQ efficacy and safety information
- PALYNZIQ dosing and administration information
- PALYNZIQ videos and resources
- PALYNZIQ patient education materials

PALYNZIQ Risk Evaluation and Mitigation Strategy (REMS) contact information:

- Phone: 1-855-758-REMS (1-855-758-7367)
- Fax: 1-866-713-8421
- Address: PALYNZIQ REMS, 200 Pinecrest Plaza, Morgantown, WV 26505-8065
- Website: PALYNZIQREMS.com



BIOMARIN Rare Connections™

Please see Important Safety Information throughout, including Boxed Warning for risk of anaphylaxis, and full Prescribing Information and Medication Guide.

BIOMARIN RARECONNECTIONS™

BioMarin RareConnections contact information:

- Phone: 1-833-PKU-CARE (1-833-758-2273)
- Email: support@biomarin-rareconnections.com
- Hours: Monday–Friday, 8 AM–8 PM ET

For additional information about BioMarin RareConnections resources and contact information, visit the website www.biomarin-rareconnections.com.

Patients interested in determining eligibility for the PALYNZIQ Co-Pay Assistance program can visit www.biomarin-rareconnections.com/copay-assistance, or call 1-833-PKU-CARE (1-833-758-2273) to speak with a BioMarin RareConnections Case Manager.

BIOMARIN Rare Connections™

Please see Important Safety Information throughout, including Boxed Warning for risk of anaphylaxis, and full Prescribing Information and Medication Guide.

NAVIGATING POTENTIAL ACCESS SCENARIOS

Access scenario	Best practice for resolution
An initial PA may be approved for 3 months to 1 year based on payer policy. During this time patients who are titrating through dose strengths may need access to multiple doses of PALYNZIQ® (pegvaliase-pqpz): 2.5 mg (NDC 68135-0058-90), 10 mg NDC (68135-0756-20), 20 mg (NDC 68135-0673-40) and 20 mg 10 pack (NDC 68135-0673-45).	Request approval for each titratable dose of 2.5 mg (NDC 68135-0058-90), 10 mg (NDC 68135-0756-20), 20 mg (NDC 68135-0673-40) and 20 mg 10 pack (NDC 68135-0673-45) on the initial PA request, if payer allows. This may prevent your clinic from needing to submit multiple PA requests at varying times during the titration.
Even with an approved PA in place for PALYNZIQ, some plans may require an override when therapy exceeds a certain quantity or cost. Some overrides can be submitted by the SP but some payers mandate that the prescriber submit the override request.	Submit the override request to the payer promptly to expedite the patient's continued treatment with PALYNZIQ. The payer may request additional clinical notes that the prescriber can provide as to why the patient needs this quantity.
Some plans might place PALYNZIQ on a prescription benefit tier with an onerous out-of-pocket cost for the patient. While PALYNZIQ may appear cost prohibitive for some patients, many plans provide a tier exception process that allows an SP or prescriber to advocate for reduced expense or lower cost-sharing for the patient.	BioMarin RareConnections™ and the SP can inform you whether a patient's insurance plan will allow for a tier exception reduction to lower the patient's out-of-pocket costs, and BioMarin RareConnections can inform you of a patient's eligibility for financial assistance options.
If there is a dosage change from the initial prescription, the plan may require a new PA.	If you send the updated prescription to the SP they may communicate that a PA is required by the payer. Promptly send in the information requested in the PA to expedite patient care. If you send the updated prescription to BioMarin RareConnections, the Case Manager will communicate with your clinic if a PA is required. Promptly send in the information requested in the PA to expedite patient care.

IMPORTANT SAFETY INFORMATION

INDICATION

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

BOXED WARNING: RISK OF ANAPHYLAXIS

- **Anaphylaxis has been reported after administration of PALYNZIQ and may occur at any time during treatment**
- **Administer the initial dose of PALYNZIQ under the supervision of a healthcare provider equipped to manage anaphylaxis, and closely observe patients for at least 60 minutes following injection. Prior to self-injection, confirm patient competency with self-administration, and patient's and observer's (if applicable) ability to recognize signs and symptoms of anaphylaxis and to administer auto-injectable epinephrine, if needed**
- **Consider having an adult observer for patients who may need assistance in recognizing and managing anaphylaxis during PALYNZIQ treatment. If an adult observer is needed, the observer should be present during and for at least 60 minutes after PALYNZIQ administration, should be able to administer auto-injectable epinephrine, and call for emergency medical support upon its use**
- **Prescribe auto-injectable epinephrine. Prior to the first dose, instruct the patient and observer (if applicable) on its appropriate use. Instruct the patient to seek immediate medical care upon its use. Instruct patients to carry auto-injectable epinephrine with them at all times during PALYNZIQ treatment**
- **PALYNZIQ is available only through a restricted program called PALYNZIQ REMS (Risk Evaluation and Mitigation Strategy). Further information, including a list of qualified pharmacies, is available at www.PALYNZIQREMS.com or by telephone at 1-855-758-REMS (1-855-758-7367)**

WARNINGS AND PRECAUTIONS

Anaphylaxis

- Signs and symptoms of anaphylaxis reported include syncope, hypotension, hypoxia, dyspnea, wheezing, chest discomfort/chest tightness, tachycardia, angioedema (swelling of face, lips, eyes, tongue), throat tightness, skin flushing, rash, urticaria, pruritus, and gastrointestinal symptoms (vomiting, nausea, diarrhea)
- Anaphylaxis generally occurred within 1 hour after injection; however, delayed episodes occurred up to 48 hours after PALYNZIQ administration
- Consider having an adult observer for patients who may need assistance in recognizing and managing anaphylaxis during PALYNZIQ treatment. If an adult observer is needed, the observer should be present during and for at least 60 minutes after PALYNZIQ administration, should be able to administer auto-injectable epinephrine, and call for emergency medical support upon its use
- Anaphylaxis requires immediate treatment with auto-injectable epinephrine. Prescribe auto-injectable epinephrine to all patients receiving PALYNZIQ and instruct patients to carry auto-injectable epinephrine with them at all times during PALYNZIQ treatment. Prior to the first dose, instruct the patient and observer (if applicable) on how to recognize the signs and symptoms of anaphylaxis, how to properly administer auto-injectable epinephrine, and to seek immediate medical care upon its use. Consider the risks associated with auto-injectable epinephrine use when prescribing PALYNZIQ. Refer to the auto-injectable epinephrine prescribing information for complete information
- Consider the risks and benefits of readministering PALYNZIQ following an episode of anaphylaxis. If the decision is made to readminister PALYNZIQ, administer the first dose under the supervision of a healthcare provider equipped to manage anaphylaxis and closely observe the patient for at least 60 minutes following the dose. Subsequent PALYNZIQ dose titration should be based on patient tolerability and therapeutic response
- Consider premedication with an H_1-receptor antagonist, H_2-receptor antagonist, and/or antipyretic prior to PALYNZIQ administration based upon individual patient tolerability

Other Hypersensitivity Reactions

- Hypersensitivity reactions other than anaphylaxis have been reported in 204 of 285 (72%) patients treated with PALYNZIQ in clinical trials
- Management of hypersensitivity reactions should be based on the severity of the reaction, recurrence of the reaction, and the clinical judgment of the healthcare provider, and may include dosage adjustment, temporary drug interruption, or treatment with antihistamines, antipyretics, and/or corticosteroids

ADVERSE REACTIONS

- The most common adverse reactions (at least 20% of patients in either treatment phase) were injection site reactions, arthralgia, hypersensitivity reactions, headache, generalized skin reactions lasting at least 14 days, nausea, abdominal pain, vomiting, cough, oropharyngeal pain, pruritus, diarrhea, nasal congestion, fatigue, dizziness, and anxiety
- Of the 285 patients exposed to PALYNZIQ in an induction/titration/maintenance regimen in clinical trials, 44 (15%) patients discontinued treatment due to adverse reactions. The most common adverse reactions leading to treatment discontinuation were hypersensitivity reactions (6% of patients) including anaphylaxis (3% of patients), angioedema (1% of patients), arthralgia (4% of patients), generalized skin reactions lasting at least 14 days (2% of patients), and injection site reactions (1% of patients)
- The most common adverse reactions leading to dosage reduction were arthralgia (15% of patients), hypersensitivity reactions (9% of patients), injection site reactions (4% of patients), alopecia (3% of patients), and generalized skin reactions lasting at least 14 days (2% of patients)
- The most common adverse reactions leading to temporary drug interruption were hypersensitivity reactions (14% of patients), arthralgia (13% of patients), anaphylaxis (4% of patients), and injection site reactions (4% of patients)
- Angioedema and serum sickness: In clinical trials, 22 out of 285 (8%) patients experienced 45 episodes of angioedema (symptoms included: pharyngeal edema, swollen tongue, lip swelling, mouth swelling, eyelid edema, and face edema) occurring independent of anaphylaxis. In clinical trials, serum sickness was reported in 7 out of 285 (2%) patients

Blood Phenylalanine Monitoring and Diet

- Obtain blood Phe concentrations every 4 weeks until a maintenance dosage is established. Periodically monitor blood Phe concentrations during maintenance therapy
- Counsel patients to monitor dietary protein and Phe intake, and adjust as directed by their healthcare provider

DRUG INTERACTIONS

Effect of PALYNZIQ on Other PEGylated Products

- In a single-dose study of PALYNZIQ in adult patients with PKU, two patients receiving concomitant injections of medroxyprogesterone acetate suspension (a formulation containing PEG 3350) experienced a hypersensitivity reaction. One of the two patients experienced anaphylaxis
- The clinical effects of concomitant treatment with different PEGylated products are unknown. Monitor patients treated with PALYNZIQ and concomitantly with other PEGylated products for hypersensitivity reactions including anaphylaxis

USE IN SPECIFIC POPULATIONS

Pregnancy and Lactation

- PALYNZIQ may cause fetal harm when administered to a pregnant woman
- Advise women who are exposed to PALYNZIQ during pregnancy or who become pregnant within one month following the last dose of PALYNZIQ that there is a pregnancy surveillance program that monitors pregnancy outcomes. Healthcare providers should report PALYNZIQ exposure and encourage these patients to report their pregnancy to BioMarin (1-866-906-6100)
- Monitor blood Phe levels in breastfeeding women treated with PALYNZIQ

Pediatric Use

- The safety and effectiveness of PALYNZIQ in pediatric patients have not been established

Geriatric Use

- Clinical studies of PALYNZIQ did not include patients aged 65 years and older

You are encouraged to report suspected adverse reactions to BioMarin at 1-866-906-6100, or to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see full Prescribing Information, with Boxed Warning for risk of anaphylaxis, and Medication Guide here.

Palynziq® (pegvaliase-pqpz) Injection

BioMarin RareConnections™

Phone: 1-833-PKU-CARE (1-833-758-2273)

Email: support@biomarin-rareconnections.com

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