HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PALYNZIQ safely and effectively. See full prescribing information for PALYNZIQ.

PALYNZIQ (pegvaliase-pqpz) injection, for subcutaneous use
Initial U.S. Approval: 2018

WARNING: ANAPHYLAXIS
See full prescribing information for complete boxed warning.

- **Anaphylaxis has been reported after administration of PALYNZIQ and may occur at any time during treatment. (5.1)**
- **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 epinephrine, if needed. (2.5)**
- **Prescribe epinephrine. Prior to 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 epinephrine with them at all times during PALYNZIQ treatment. (2.5, 5.1)**
- **PALYNZIQ is available only through a restricted program called the PALYNZIQ REMS. (5.2)**

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	2/2026
Dosage and Administration (2.2, 2.3, 2.4)	2/2026
Warnings and Precautions, Anaphylaxis (5.1)	2/2026
Warnings and Precautions, Other Hypersensitivity Reactions (5.3)	2/2026
Warnings and Precautions, Injection Site Infections (5.4)	10/2025
Warnings and Precautions, Hypophenylalaninemia (5.5)	2/2026

----------INDICATIONS AND USAGE----------
PALYNZIQ is a phenylalanine (Phe)-metabolizing enzyme indicated to 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. (1)

----------DOSAGE AND ADMINISTRATION----------
- Obtain baseline blood Phe concentration before initiating treatment. (2.1)
- Consider premedication for hypersensitivity reactions. (2.1, 5.1, 5.3)
- The recommended initial dosage for PALYNZIQ is 2.5 mg subcutaneously once weekly for 4 weeks. (2.2)
- See the Full Prescribing Information for titration, maintenance, discontinuation, and dose reduction. (2.2)
- See Full Prescribing Information for dosage and administration modifications due to anaphylaxis. (2.3)
- Obtain blood Phe concentrations every 4 weeks until a maintenance dosage is established. (2.4)
- Periodically monitor blood Phe concentrations during maintenance therapy and monitor dietary protein and phenylalanine intake throughout treatment. (2.4)
- Rotate injection sites. If more than one injection is needed for a single dose, the injection sites should be at least 2 inches away from each other. (2.5)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 2.5 mg/0.5 mL, 10 mg/0.5 mL, and 20 mg/mL in a single-dose prefilled syringe. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------
- *Hypersensitivity Reactions, Other than Anaphylaxis*: Management should be based on the severity of the reaction, recurrence, and clinical judgement. (5.3)
- *Injection Site Infections*: Serious injection site infections, including abscess, cellulitis, necrosis, and ulcer have been reported. Instruct patients to contact their healthcare provider if signs or symptoms of an infection develop, persist, or worsen. (5.4)
- *Hypophenylalaninemia*: Some PKU patients treated with PALYNZIQ have experienced hypophenylalaninemia; monitor blood Phe levels periodically during treatment. (5.5)

----------ADVERSE REACTIONS----------
- Most common adverse reactions (at least 20% in either treatment phase) are: 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. (6.1)
- Most common adverse reactions in patients who are 12 to less than 18 years of age (at least 20% and greater than in control) are: injection site reactions, arthralgia, headache, pyrexia, hypersensitivity reactions, dizziness, nausea, vomiting, fatigue, and pain in extremity. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact BioMarin Pharmaceutical Inc. at 1-866-906-6100, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Effect of PALYNZIQ on Other PEGylated Products: Monitor for hypersensitivity reactions, including anaphylaxis, with concomitant treatment. (7.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 2/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: ANAPHYLAXIS

- **Anaphylaxis has been reported after administration of PALYNZIQ and may occur at any time during treatment *[see Warnings and Precautions (5.1)]*.**
- **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 administer epinephrine, if needed *[see Dosage and Administration (2.5)]*.**
- **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 epinephrine, and call for emergency medical support upon its use *[see Warnings and Precautions (5.1)]*.**
- **Prescribe epinephrine to all patients treated with PALYNZIQ. Prior to the first dose, instruct the patient and observer (if applicable) how to recognize the signs and symptoms of anaphylaxis, how to properly administer epinephrine, and to seek immediate medical care upon its use. Instruct patients to carry epinephrine with them at all times during treatment with PALYNZIQ *[see Dosage and Administration (2.5) and Warnings and Precautions (5.1)]*.**
- **Consider the risks and benefits of readministering PALYNZIQ following an episode of anaphylaxis. If the decision is made to readminister PALYNZIQ, readminister 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 *[see Dosage and Administration (2.5) and Warnings and Precautions (5.1)]*.**
- **Because of the risk of anaphylaxis, PALYNZIQ is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the PALYNZIQ REMS *[see Warnings and Precautions (5.2)]*.**

1 INDICATIONS AND USAGE

PALYNZIQ is indicated to 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.

2 DOSAGE AND ADMINISTRATION

2.1 Important Recommendation Prior to PALYNZIQ Treatment

- Treatment with PALYNZIQ should be managed by a healthcare provider experienced in the management of PKU.

- Obtain baseline blood phenylalanine concentration before initiating treatment.

- Consider premedication with an H_1-receptor antagonist, H_2-receptor antagonist, and/or antipyretic based upon individual patient tolerability *[see Warnings and Precautions (5.1, 5.3)]*.

2.2 Recommended Dosage and Administration

Induction
The recommended initial induction dosage for PALYNZIQ is 2.5 mg subcutaneously once weekly for 4 weeks. Administer the initial dose under the supervision of a healthcare provider *[see Dosage and Administration (2.5)].*

Titration
Titrate the PALYNZIQ dosage in a step-wise manner, based on tolerability, over at least 5 weeks, to achieve a dosage of 20 mg subcutaneously once daily according to Table 1.

Maintenance
Therapeutic response may not be achieved until the patient is titrated to an effective maintenance dosage of PALYNZIQ. Use the lowest effective and tolerated dosage of PALYNZIQ.

Assess patient tolerability, blood phenylalanine concentrations, and dietary protein and phenylalanine intake throughout treatment.

Individualize the maintenance dosage to achieve blood phenylalanine control (blood phenylalanine concentrations less than or equal to 600 micromol/L), taking into account patient tolerability to PALYNZIQ and dietary protein and phenylalanine intake (see Table 1).

Maintain the PALYNZIQ dosage at 20 mg once daily for at least 24 weeks. Consider increasing the PALYNZIQ dosage to 40 mg once daily in patients who have been on 20 mg once daily continuously for at least 24 weeks without achieving blood phenylalanine control. Consider increasing the PALYNZIQ dosage to a maximum of 60 mg once daily in patients who have been on 40 mg once daily continuously for at least 16 weeks without achieving blood phenylalanine control.

Discontinuation
Discontinue PALYNZIQ in patients who have not achieved an adequate response after 16 weeks of continuous treatment with the maximum dosage of 60 mg once daily *[see Clinical Studies (14)].*

Table 1: Recommended Dosing Regimen

Treatment	PALYNZIQ Dosage	Duration[1]
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[2]	20 mg once daily	24 weeks
	40 mg once daily	16 weeks
Maximum[3]	60 mg once daily	16 weeks

[1] Additional time may be required prior to each dosage escalation based on patient tolerability.
[2] 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)]*.
[3] 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.

Dose Reduction
During titration and maintenance of PALYNZIQ treatment, patients may experience blood phenylalanine concentrations below 30 micromol/L. For blood phenylalanine concentrations below 30 micromol/L, the dosage of PALYNZIQ may be reduced and/or dietary protein and phenylalanine intake may be modified to maintain blood phenylalanine concentrations within a clinically acceptable range and above 30 micromol/L *[see Warning and Precaution (5.5)]*.

Missed Dose
If a dose is missed, instruct patients to take their next dose as scheduled and to not take two doses of PALYNZIQ to make up for the missed dose.

2.3 Dosage and Administration Modifications Due to Anaphylaxis

If the decision is made to readminister PALYNZIQ after an anaphylaxis episode, administer the first dose following the anaphylaxis episode 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 dose titration should be based on patient tolerability and therapeutic response *[see Warnings and Precautions (5.1)]*.

2.4 Blood Phenylalanine Monitoring and Diet

After initiating treatment with PALYNZIQ, obtain blood phenylalanine concentrations every 4 weeks until a maintenance dosage is established. After a maintenance dosage is established, periodic blood phenylalanine monitoring is recommended to assess blood phenylalanine control. Frequent blood Phe monitoring is recommended in the pediatric population.

Monitor patients' dietary protein and phenylalanine intake throughout treatment with PALYNZIQ and counsel them on how to adjust their dietary protein and phenylalanine intake, as needed, based on blood phenylalanine concentrations.

2.5 Administration Instructions

- Each prefilled syringe of PALYNZIQ is intended for use as a single subcutaneous injection.

- Inspect PALYNZIQ visually for particulate matter and discoloration prior to administration. PALYNZIQ is a clear to slightly opalescent, colorless to pale yellow solution. Discard if discolored, cloudy, or if particulate matter is present.

- Prior to first dose of PALYNZIQ, prescribe epinephrine, and instruct the patient and observer (if applicable) on how to recognize the signs and symptoms of anaphylaxis, how to properly administer epinephrine, and to seek immediate medical care upon its use.

- Perform initial administration(s) and/or readministration after an anaphylaxis episode under the supervision of a healthcare provider equipped to manage anaphylaxis, and closely observe patients for at least 60 minutes following injection *[see Warnings and Precautions (5.1)]*. Prior to self-injection,

confirm patient competency with self-administration using aseptic technique. Discard after use.

- 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 each PALYNZIQ administration, should be able to administer epinephrine, and call for emergency medical support upon its use *[see Warnings and Precautions (5.1)]*.

- The recommended injection sites for PALYNZIQ are: the front middle of thighs and the abdomen at least 2 inches (five centimeters) away from the navel. If a caregiver is giving the injection, the top of the buttocks and the back of the upper arms are also appropriate injection sites.

- Do not inject PALYNZIQ into moles, scars, birthmarks, bruises, rashes, or areas where the skin is hard, tender, red, damaged, burned, inflamed, or tattooed. Check the injection site for redness, swelling, or tenderness.

- Rotate sites for subcutaneous injections of PALYNZIQ. If more than one injection is needed for a single dose of PALYNZIQ, the injection sites should be at least 2 inches away from each other. The second injection site can be on the same part of the body or a different part of the body.

3 DOSAGE FORMS AND STRENGTHS

PALYNZIQ is a clear to slightly opalescent, colorless to pale yellow solution available as follows:
- Injection: 2.5 mg/0.5 mL single-dose prefilled syringe
- Injection: 10 mg/0.5 mL single-dose prefilled syringe
- Injection: 20 mg/mL single-dose prefilled syringe

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis

In PALYNZIQ Studies 1, 2, and 3 with an induction/titration/maintenance dosage regimen, 10% (29/285) of PALYNZIQ-treated patients experienced a total of 42 anaphylaxis episodes *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.6)]*. The exposure-adjusted rate of anaphylaxis was highest during the induction and titration phases (0.25 episodes/person-years; 5% of PALYNZIQ-treated patients with at least one episode) and decreased in the maintenance phase (0.05 episodes/person-years; 7% of PALYNZIQ-treated patients with at least one episode). Signs and symptoms of anaphylaxis reported in PALYNZIQ-treated patients included 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 occurred within 1 hour after injection in 81% of PALYNZIQ-treated patients (34/42 episodes); however, delayed episodes also occurred up to 48 hours after PALYNZIQ administration. Anaphylaxis occurred within the first year of dosing in 69% of PALYNZIQ-treated patients (29/42 episodes), but cases also occurred after one year of dosing and up to 1,604 days (4.4 years) into treatment. Management of anaphylaxis in PALYNZIQ-treated patients included: administration of epinephrine (48%; 20/42 episodes), corticosteroids (55%; 23/42 episodes),

antihistamines (57%; 24/42 episodes), and/or oxygen (5%; 2/42 episodes). In these trials, 72% (21/29) of patients who experienced anaphylaxis were rechallenged with PALYNZIQ and 29% (6/21) of patients who were rechallenged had recurrence of anaphylaxis. All anaphylaxis episodes resolved without sequelae.

In Study 4, conducted in patients who were 12 to less than 18 years of age *[see Clinical Trials (14)],* premedication was administered to all patients. A single episode of anaphylaxis, was reported in 11% (4/36) of PALYNZIQ-treated patients with symptoms similar to those reported in the adult clinical trials. All 4 patients were managed with administration of epinephrine. Treatment with PALYNZIQ was discontinued in two patients and the other two patients were rechallenged with PALYNZIQ without recurrence of anaphylaxis.

Steps to Take to Prevent, Mitigate, Monitor for, and Manage Anaphylaxis
Prior to PALYNZIQ administration, consider premedication with an H_1-receptor antagonist, H_2-receptor antagonist, and/or antipyretic based upon individual patient tolerability.

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 epinephrine, and call for emergency medical support upon its use.

Anaphylaxis requires immediate treatment with epinephrine. Prescribe epinephrine to all PALYNZIQ-treated patients while considering the risks associated with epinephrine use (refer to the epinephrine prescribing information for complete information). Instruct patients to carry epinephrine with them at all times during PALYNZIQ treatment. Prior to the first PALYNZIQ dose, instruct the patient and observer (if applicable) on how to recognize the signs and symptoms of anaphylaxis, how to properly administer epinephrine, and to seek immediate medical care upon its use.

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.

PALYNZIQ is available only through a restricted program under a REMS *[see Warnings and Precautions (5.2)].*

5.2 PALYNZIQ REMS

PALYNZIQ is available only through a restricted program under a REMS called the PALYNZIQ REMS because of the risk of anaphylaxis *[see Warnings and Precautions (5.1)].*

Notable requirements of the PALYNZIQ REMS include the following:
- Prescribers must be certified with the program by enrolling in the program and completing training.
- Prescribers must prescribe 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 have epinephrine available at all times while taking PALYNZIQ.

Further information, including a list of qualified pharmacies, is available at www.PALYNZIQREMS.com or by telephone 1-855-758-REMS (1-855-758-7367).

5.3 Other Hypersensitivity Reactions

In Studies 1, 2, and 3 of PALYNZIQ with induction/titration/maintenance dosage regimen, hypersensitivity reactions, other than anaphylaxis *[see Warnings and Precautions (5.1), Adverse Reactions (6.1), and Immunogenicity (12.6)],* have been reported in 72% (204/285) PALYNZIQ-treated patients. The exposure adjusted rate of other hypersensitivity reactions was highest during the induction and titration phases (4.3 episodes/person-year; 50% of PALYNZIQ-treated patients with at least one adverse reaction) and decreased in the maintenance phase (1.3 episodes/person-year; 61% of PALYNZIQ-treated patients with at least one adverse reaction).

Hypersensitivity reactions generally occurred more frequently in PALYNZIQ-treated patients with higher anti-pegvaliase-pqpz antibody titers *[see Clinical Pharmacology (12.6)].*

In Study 4, hypersensitivity reactions other than anaphylaxis were reported in 33% (12/36) of PALYNZIQ-treated patients who were 12 to less than 18 years of age. The exposure adjusted rate of other hypersensitivity reactions during the induction and titration phases was 1 episodes/person-year; 3/36 (8%) of PALYNZIQ-treated patients had at least one adverse reaction. The exposure adjusted rate of other hypersensitivity reactions during the maintenance phase was 1.4 episodes/person-year; 11/34 (32%) of PALYNZIQ-treated patients had at least one adverse reaction.

Prior to PALYNZIQ administration, consider premedication with an H_1-receptor antagonist, H_2-receptor antagonist, and/or antipyretic based upon individual patient tolerability *[see Dosage and Administration (2.1)]*. Management of hypersensitivity reactions should be based on the severity of the reaction, recurrence of the reaction, and the clinical judgement of the healthcare provider, and may include dosage adjustment, temporary drug interruption, or treatment with antihistamines, antipyretics, and/or corticosteroids.

5.4 Injection Site Infections

Serious injection site infections including abscess, cellulitis, necrosis, and ulcer have been reported with PALYNZIQ in clinical trials and in the postmarketing setting. Some cases required hospitalization, surgical debridement, intravenous antibiotics, and discontinuation of PALYNZIQ. Provide proper training to patients and/or caregivers on the use of aseptic injection technique. Advise patients to rotate injection sites with each dose and to check the site for redness, swelling, or tenderness. Instruct patients to contact their healthcare provider if signs or symptoms of an infection develop, persist, or worsen. Advise patients to not administer PALYNZIQ into the affected area until the infection has resolved *[see Dosage and Administration (2.5) and Adverse Reactions (6.1, 6.2)].*

5.5 Hypophenylalaninemia

In clinical trials of PALYNZIQ, some PKU patients have experienced hypophenylalaninemia (low blood Phe), including some patients with prolonged low blood Phe levels, during treatment with PALYNZIQ *[see Adverse Reactions (6.1)]*. Prolonged levels of blood Phe that are too low have been associated with catabolism and endogenous protein breakdown, which has been associated with adverse developmental outcomes.

Monitor blood Phe levels periodically during treatment. During titration and maintenance of PALYNZIQ treatment, patients may experience blood phenylalanine concentrations below 30 micromol/L *[Adverse Reactions (6.1)]*. For blood phenylalanine concentrations below 30 micromol/L, the dosage of PALYNZIQ may be reduced and/or dietary protein and phenylalanine intake may be modified to maintain blood phenylalanine concentrations within a clinically acceptable range and above 30 micromol/L. Frequent blood Phe monitoring is recommended in the pediatric population.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed below and in other sections of labeling:

- Anaphylaxis *[see Warnings and Precautions (5.1)]*
- Other Hypersensitivity Reactions *[see Warnings and Precautions (5.3)]*
- Injection Site Infections *[see Warnings and Precautions (5.4)]*
- Hypophenylalaninemia *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Trials With Induction/Titration/Maintenance Dosage Regimen in Patients With PKU (Study 1, Study 2, and Study 3)

The data described below reflect a total treatment exposure of 789 patient-years in 285 patients who received PALYNZIQ in an induction/titration/maintenance regimen in a pooled safety analysis of a phase 2 study (Study 1), and 2 phase 3 studies (Studies 2 and 3, respectively) *[see Clinical Studies (14)]*. Twelve patients aged 16-17 years at enrollment received PALYNZIQ as part of the overall induction/titration/maintenance population and are included in this analysis. Of the 285 patients, 229 patients were exposed to PALYNZIQ for 24 weeks, 209 patients were exposed for 1 year, 181 patients were exposed for 2 years, and 160 patients were exposed for 3 years or longer. The patient population was evenly distributed between male and female patients, the mean age was 29 years (range: 16 to 56 years), and 98% of patients were White.

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 from the pooled safety analysis, 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).

Table 2 lists adverse reactions reported in at least 15% of patients treated with PALYNZIQ in an induction/titration/maintenance dosage regimen in clinical trials and illustrates the adverse reaction rates over time by treatment phase. Table 3 lists laboratory abnormalities reported in at least 10% of patients treated with PALYNZIQ in this pooled safety analysis.

For these analyses, the induction/titration phase was defined as the time prior to reaching a stable dose (completing an 8-week phase at the same dose level). Once a stable dosage was reached, patients were considered to be in the maintenance phase thereafter. Safety data for patients who reached the maintenance phase are included within either the induction/titration or maintenance phases depending on the onset date of the adverse reaction. Safety data for patients who did not reach the maintenance phase are included within the induction/titration phase. The maintenance phase includes data for patients who were previously on PALYNZIQ and transitioned to placebo during the randomized withdrawal period of Study 3 *[see Clinical Studies (14)].*

Rates of adverse reactions (adjusted for duration of exposure) generally decreased over time and for some stayed relatively stable. In the maintenance phase, the rate of adverse reactions (adjusted for duration of exposure) in patients who reached the maintenance phase was comparable across dosages evaluated. The types and rate of adverse reactions reported during the maintenance phase in patients who received 20 mg once daily, 40 mg once daily, and 60 mg once daily were similar. During long-term treatment (greater than 36 months), the exposure-adjusted rates of adverse reactions decreased.

Rates of laboratory abnormalities (adjusted for duration of exposure) stayed relatively stable over time, except for complement C4 below lower limit of normal (LLN) and high sensitivity-C Reactive Protein (hs-CRP) above 0.287 mg/dL over a 6-month period (both decreased over time) and hypophenylalaninemia (blood phenylalanine concentration below 30 micromol/L) on a single measurement (increased over time). There were no dose-related trends in type or rate of laboratory abnormalities (adjusted for duration of exposure) reported during the maintenance phase in patients receiving 20 mg once daily, 40 mg once daily, or 60 mg once daily.

Table 2: Adverse Reactions* Reported in at Least 15% of PKU Patients Treated with PALYNZIQ in an Induction/Titration/Maintenance Regimen in Studies 1, 2, and 3 – Incidence and Exposure-Adjusted Rates

Treatment Phase Treatment Duration	**Induction/Titration Phase (N = 285)** 141 person-years Mean: 188 days Median: 116 days Range: 1 to 2266 days		**Maintenance Phase (N = 225)** 652 person-years Mean: 1087 days Median: 1158 days Range: 5 to 2017 days	
Adverse Reaction	**N (%)[1]**	**Episodes (Rate)[1]**	**N (%)[1]**	**Episodes (Rate)[1]**
Injection site reactions[2]	252 (88%)	2965 (21)	166 (74%)	2169 (3.3)
Arthralgia[3]	211 (74%)	1049 (7.4)	154 (68%)	893 (1.4)
Hypersensitivity reactions[4]	153 (54%)	634 (4.5)	145 (64%)	845 (1.3)
Headache[5]	102 (36%)	214 (1.5)	126 (56%)	1049 (1.6)
Generalized skin reaction lasting at least 14 days[6]	61 (21%)	97 (0.7)	93 (41%)	186 (0.3)
Nausea	52 (18%)	68 (0.5)	69 (31%)	141 (0.2)
Abdominal pain[7]	39 (14%)	54 (0.4)	67 (30%)	162 (0.3)
Vomiting	36 (13%)	53 (0.4)	68 (30%)	139 (0.2)
Cough	27 (9%)	33 (0.2)	67 (30%)	100 (0.2)
Oropharyngeal pain	38 (13%)	45 (0.3)	65 (29%)	108 (0.2)
Pruritus	58 (20%)	102 (0.7)	61 (27%)	424 (0.7)
Diarrhea	26 (9%)	32 (0.2)	61 (27%)	116 (0.2)
Nasal congestion	12 (4%)	16 (0.1)	61 (27%)	87 (0.1)
Fatigue	37 (13%)	81 (0.6)	55 (24%)	110 (0.2)
Dizziness	47 (16%)	65 (0.5)	48 (21%)	100 (0.2)
Anxiety	14 (5%)	23 (0.2)	48 (21%)	100 (0.2)
Alopecia	13 (5%)	14 (0.1)	43 (19%)	62 (0.1)

* ≥ 15% incidence in either treatment phase

[1] N (%) = Number of patients with at least 1 Adverse Reaction (%); Rate = Exposure-Adjusted Rate of Adverse Reactions (Adverse Reactions/Person-Years)

[2] Includes injection site: reaction, erythema, pruritus, pain, bruising, rash, swelling, urticaria, induration, hemorrhage, edema, mass, inflammation, nodule, discoloration, warmth, hematoma, irritation, vesicles, hypersensitivity, papule, discomfort, scar, paresthesia, hypertrophy, extravasation, dryness, scab

[3] Includes arthralgia, pain in extremity, back pain, musculoskeletal pain, neck pain

[4] Includes rash, urticaria, anaphylaxis, rash generalized, hypersensitivity, rash erythematous, rash maculo-papular, rash pruritic, serum sickness, swelling face, dermatitis contact, swollen tongue, lip swelling, rash macular, pharyngeal edema, injection site hypersensitivity, eczema, drug eruption, dermatitis allergic, dermatitis, tongue edema, palatal edema, edema mouth, multiple allergies, lip edema, eye edema, exfoliative rash, drug hypersensitivity, dermatitis atopic, dermatitis acneiform, pruritus allergic, mouth swelling, implant site rash, gingival swelling, face edema, eyelid edema, eye swelling, dermatitis psoriasiform, dermatitis infected, conjunctivitis allergic, bronchospasm, angioedema, allergic sinusitis, allergic cough, eczema nummular, rhinitis allergic

[5] Includes headache, migraine, sinus headache

[6] Includes pruritus, rash, urticaria, dry skin, rash erythematous, erythema, cellulitis, rash macular, pruritus generalized, petechiae, dermatitis allergic, skin infection, skin induration, rash maculo-papular, rash generalized, pharyngeal edema, macule, granulomatous dermatitis, exfoliative rash, drug eruption, dermatitis atopic, dermatitis, xanthogranuloma, skin plaque, skin mass, skin lesion, skin hypopigmentation, skin hyperpigmentation, skin exfoliation, septal panniculitis, scar, rash pruritic, rash papular, psoriatic arthropathy, pruritus allergic, papule, necrobiosis lipoidica diabeticorum, furuncle, eczema, ecchymosis, dermatitis psoriasiform, dermatitis infected, blister, eczema nummular, granuloma, infected dermal cyst, lipohypertrophy, psoriasis, skin irritation

[7] Includes abdominal pain, abdominal pain upper, abdominal discomfort

Table 3: Laboratory Abnormalities Reported in at Least 10% of PKU Patients Treated with PALYNZIQ in an Induction/Titration/Maintenance Regimen in Studies 1, 2, and 3 – Incidence and Exposure-Adjusted Rates

Treatment Phase Treatment Duration	**Induction/Titration Phase (N = 285)** 141 person-years Mean: 188 days Median: 116 days Range: 1 to 2266 days		**Maintenance Phase (N = 225)** 652 person-years Mean: 1087 days Median: 1158 days Range: 5 to 2017 days	
Laboratory Measurement	**N (%)[1]**	**Episodes (Rate)[1]**	**N (%)[1]**	**Episodes (Rate)[1]**
Complement factor C3 below LLN	195 (68%)	453 (3.2)	188 (84%)	2259 (3.5)
C-reactive protein (CRP) above ULN	182 (64%)	359 (2.5)	160 (71%)	1414 (2.2)
Hypophenylalaninemia[2] on a single measurement	53 (19%)	216 (1.5)	147 (65 %)	1553 (2.4)
Complement factor C4 below LLN	177 (62%)	318 (2.3)	111 (49%)	714 (1.1)
Hypophenylalaninemia[2] on 2 or more consecutive measurements	45 (16%)	62 (0.4)	111 (49%)	204 (0.3)
Blood creatine phosphokinase (CPK) above ULN	50 (18%)	88 (0.6)	108 (48%)	377 (0.6)
Hs-CRP above 0.287 mg/dL over a 6 month period	34 (12%)	34 (0.4)	36 (16%)	46 (0.1)

[1] N (%) = Number of patients with at least 1 laboratory abnormality (%); Rate = Exposure-Adjusted Rate of Laboratory Abnormalities (Laboratory Abnormalities/Person-Years)
[2] Blood phenylalanine concentration below 30 micromol/L
LLN – lower limit of normal
ULN – upper limit of normal
Hs – high sensitivity

Description of Selected Adverse Reactions

Arthralgia
In clinical trials, 245 out of 285 (86%) patients experienced episodes consistent with arthralgia (includes back pain, musculoskeletal pain, pain in extremity, and neck pain).

Arthralgia episodes were more frequent during the induction/titration phase (7.4 episodes/patient-year) and decreased over time (1.4 episodes/patient-year in the maintenance phase).

Forty-four out of 285 (15%) patients had one episode of arthralgia, 32 (11%) patients had 2 episodes of arthralgia, 18 (6%) had 3 episodes of arthralgia, and 146 (51%) had 4 or more episodes of arthralgia. Arthralgia occurred as early as after the first dose of PALYNZIQ and occurred at any time during treatment. The mean duration of arthralgia was 16 days (median: 3 days, range: 1 to 936 days), and 19% of arthralgia episodes had a duration of at least 14 days. Severe arthralgia (severe pain limiting self-care activities of daily living) was reported by 11 (4%) patients. In addition to arthralgia, other joint-related signs and symptoms reported were: joint swelling (24 patients; 8%), joint stiffness (22 patients; 8%), and musculoskeletal stiffness (20 patients; 7%). Arthralgia episodes were managed with medications (e.g., nonsteroidal anti-inflammatory drugs, glucocorticoids, and acetaminophen), PALYNZIQ dosage reduction (4% of episodes), PALYNZIQ interruption (4% of episodes), or PALYNZIQ withdrawal (0.6% of episodes). 97% of arthralgia episodes were reported as resolved at the time of last observation (up to 77 months of follow-up).

Injection Site Reactions
Injection site reactions were reported as early as after the first dose of PALYNZIQ and occurred at any time during treatment. Injection site reactions were more frequent during the induction/titration phase

(21 episodes/patient-years) and decreased over time (3 episodes/patient-years in the maintenance phase). The mean duration of injection site reaction was 10 days (median: 2 days, range: 1 to 1612 days), and 8% of injection site reactions had a duration of at least 14 days. 99% of injection site reactions were reported as resolved at the time of last observation (up to 77 months of follow-up).

Three injection site reactions consistent with granulomatous skin lesions were reported (each reaction occurring in one patient): granulomatous dermatitis (occurred after 464 days of PALYNZIQ treatment and lasted 16 days), xanthogranuloma (occurred after 378 days of PALYNZIQ treatment and lasted 638 days) was treated with a topical antihistamine, corticosteroid, and PALYNZIQ treatment was discontinued, and necrobiosis lipoidica diabeticorum (occurred after 281 days of PALYNZIQ treatment and lasted 281 days). Necrobiosis lipoidica diabeticorum was treated with steroid injections and complicated by *Pseudomonas* infection. All three injection site reactions resolved.

One patient reported soft tissue infection (occurred after 196 days of PALYNZIQ treatment and lasted 8 days) associated with mesenteric panniculitis treated with antibiotics which resulted in treatment discontinuation.

Generalized Skin Reactions (not limited to the injection site) Lasting at Least 14 Days
In clinical trials, 134 out of 285 (47%) patients treated with PALYNZIQ experienced generalized skin reactions (not limited to the injection site) lasting at least 14 days. Mean duration of these reactions was 63 days (median: 37 days; range: 14 to 638 days). Generalized skin reactions were more frequent during the induction/titration phase (0.7 episodes/patient-years) and decreased over time (0.3 episodes/patient-years in the maintenance phase).

The mean time from first dose of PALYNZIQ to onset of skin reactions was 373 days (median: 213 days; range: 2 to 1970 days). 5% of these reactions persisted at least 180 days, and 86% of these reactions were reported as resolved at the time of last observation (up to 77 months of follow-up).

Angioedema
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. Angioedema (included under Hypersensitivity in Table 2) was more frequent during the induction/titration phase (0.14 episodes/patient-year) and decreased over time (0.04 episodes/patient-year in the maintenance phase). Three patients discontinued treatment. All episodes resolved. Angioedema can present as a symptom of anaphylaxis *[see Warnings and Precautions (5.1)]*.

Serum Sickness
In clinical trials, serum sickness was reported in 7 out of 285 (2%) patients. Serum sickness episodes were more frequent during the induction/titration phase (0.04 episodes/patient-year) and decreased over time (less than 0.01 episodes/patient-year during the maintenance phase). All serum sickness reactions resolved without sequelae (duration of serum sickness ranged from 1 to 8 days). Out of the 7 patients who experienced serum sickness, 5 patients continued treatment without a recurrence and managed serum sickness with drug interruption, dosage reduction and/or concomitant medication. Two patients discontinued treatment.

<u>Clinical Trial in Patients who are 12 to Less Than 18 Years of Age With PKU (Study 4)</u>
The safety of PALYNZIQ in patients who are 12 to less than 18 years of age was evaluated in Study 4, which was an open label, randomized study in 55 patients with PKU. Patients were randomized in a 2:1 ratio to receive PALYNZIQ in an induction/titration/maintenance regimen or to continue dietary management only for 72 weeks *[see Clinical Studies (14)]*.

In Study 4, the total exposure to PALYNZIQ was 45.4 person-years in 36 patients *[see Clinical Trials (14)]* with a mean (SD) daily dose of 21 (10) mg, mean (SD) total duration of 461 (151) days, and a median duration of 518 days. Of the 36 patients, anaphylaxis was reported in 4 (11%) and 2 (6%) discontinued from the study due to anaphylaxis *[see Warnings and Precautions (5.1)]*. A total of 19 (53%) patients reported dose interruption and the most common adverse reactions leading to dose interruption were arthralgia (n=8) and headache (n=4). Dose reductions were reported in 9 (25%) patients and was most commonly due to arthralgia (n=4) and hypophenylalaninemia (n=3).

The most common adverse reactions in patients who are 12 to less than 18 years of age (at least 20% and greater than in control) were injection site reactions, arthralgia, headache, pyrexia, hypersensitivity reactions, dizziness, nausea, vomiting, fatigue, and pain in extremity.

Table 4 lists the adverse reactions that were reported in at least 15% of patients treated with PALYNZIQ and greater than that of the diet-only arm in Study 4.

Table 4: Adverse Reactions Reported in at Least 15% of PKU Patients Treated with PALYNZIQ and Greater Than the Diet-Only Arm in Study 4

Adverse Reaction	**PALYNZIQ N = 36 (%)**	**DIET-ONLY N = 19 (%)**
Injection site reactions[1]	31 (86)	0 (0)
Arthralgia	27 (75)	1 (5)
Headache	24 (67)	8 (42)
Pyrexia	15 (42)	1 (5)
Hypersensitivity reactions[2]	15 (42)	2 (11)
Dizziness	11 (31)	2 (11)
Nausea	11 (31)	3 (16)
Vomiting	10 (28)	2 (11)
Fatigue	8 (22)	2 (11)
Pain in extremity	8 (22)	2 (11)
Myalgia	7 (19)	1 (5)
Erythema	6 (17)	0
Back pain	6 (17)	3 (16)

[1] Injection site reactions include injection site: reaction, erythema, pruritus, pain, bruising, rash, swelling, urticaria, induration, hemorrhage, edema, mass, inflammation, nodule, discoloration, warmth, hematoma, irritation, vesicles, hypersensitivity, papule, discomfort, scar, paresthesia, hypertrophy, extravasation, dryness, scab.

[2] Hypersensitivity includes rash, urticaria, anaphylactic reaction, rash generalized, hypersensitivity, rash erythematous, rash maculo-papular, rash pruritic, serum sickness, swelling face, dermatitis contact, swollen tongue, lip swelling, rash macular, pharyngeal edema, injection site hypersensitivity, eczema, drug eruption, dermatitis allergic, dermatitis, tongue edema, palatal edema, edema mouth, multiple allergies, lip edema, eye edema, exfoliative rash, drug hypersensitivity, dermatitis atopic, dermatitis acneiform, pruritus allergic, mouth swelling, implant site rash, gingival swelling, face edema, eyelid edema, eye swelling, dermatitis psoriasiform, dermatitis infected, conjunctivitis allergic, bronchospasm, angioedema, allergic sinusitis, allergic cough, eczema nummular, rhinitis allergic.

Laboratory Abnormalities

Eosinophilia: In Study 4, 44% of patients in the PALYNZIQ-treated group experienced eosinophilia above the ULN compared to 11% of patients in the diet-only group.

Hypophenylalaninemia: In Study 4, 28% of patients in the PALYNZIQ-treated group experienced hypophenylalaninemia, defined as blood Phe level < 30 µmol/L on 1 or more measurements, compared to 5% of patients in the diet-only group.

Creatine Phosphokinase (CPK) Elevation: In Study 4, 14% of patients in the PALYNZIQ-treated group experienced CPK level greater than 3 times the ULN compared to 0% of patients in the diet-only group.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of PALYNZIQ. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Administration site conditions: injection site infection, cellulitis, necrosis, and abscess.

7 DRUG INTERACTIONS

7.1 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 a hypersensitivity reaction on day 15 after a single PALYNZIQ dosage of 0.67 mg within 15 minutes following medroxyprogesterone acetate injectable suspension, and subsequently experienced anaphylaxis on day 89 within 30 minutes after the next dose of medroxyprogesterone acetate injectable suspension. The other patient experienced a hypersensitivity reaction on day 40 after a single PALYNZIQ dosage of 0.08 mg within 10 minutes following medroxyprogesterone acetate injectable suspension. Both patients had high anti-PEG IgG antibody titers at or around the time of the hypersensitivity reactions.

In PALYNZIQ clinical trials, the majority of patients developed anti-PEG IgM and IgG antibodies after treatment with PALYNZIQ *[see Clinical Pharmacology (12.6)]*. The clinical effects of concomitant treatment with different PEGylated products is unknown. Monitor patients treated with PALYNZIQ and concomitantly with other PEGylated products for hypersensitivity reactions including anaphylaxis.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from pharmacovigilance and published literature with pegvaliase-pqpz use in pregnant women have not identified a clear association with major birth defects, miscarriage or other adverse maternal or fetal outcomes *(see Data)*.

There are risks to the fetus associated with poorly controlled phenylalanine concentrations in women with PKU during pregnancy including increased risk for miscarriage, major birth defects (including microcephaly and major cardiac malformations), intrauterine fetal growth retardation, and future intellectual disability with low IQ; therefore, phenylalanine concentrations should be closely monitored in women with PKU during pregnancy *(see Clinical Considerations and Data).* Advise pregnant women of the potential risks to the fetus.

A reproduction study in pregnant rabbits without PKU treated with pegvaliase-pqpz demonstrated a high incidence of fetal malformations throughout the skeletal system, and in kidneys, lungs, and eyes. Embryo-fetal toxicity (increased resorptions and reduced fetal weight) was also observed. These effects occurred at 5 times the maximum recommended daily dose and were associated with strong signs of maternal toxicity, including marked reductions in weight gain and food consumption, and death. A reproduction study in pregnant rats without PKU treated with pegvaliase-pqpz demonstrated an increase in skeletal variations with no malformations observed. The effects in rats occurred at 2.8 times the maximum recommended daily dose. In a pre-/post-natal development study in rats, pegvaliase-pqpz produced reduced survival of offspring during lactation, decreases in pup weight and litter size, and delayed sexual maturation of offspring when administered daily at 13 times the maximum recommended daily dose. Observed embryofetal and postnatal findings could be attributable to maternal toxicity.

All pregnancies have a background risk of major birth defects, pregnancy loss, or other adverse pregnancy outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. The estimated background risk of major birth defects and miscarriage in pregnant women with PKU who maintain blood phenylalanine concentrations greater than 600 micromol/L during pregnancy is 12-73% and 24%, respectively.

There is a pregnancy surveillance program for PALYNZIQ. If PALYNZIQ is administered during pregnancy, or if a patient becomes pregnant while receiving PALYNZIQ or within one month following the last dose of PALYNZIQ, healthcare providers should report PALYNZIQ exposure by calling 1-866-906-6100.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-Fetal Risk

Uncontrolled blood phenylalanine concentrations above 600 micromol/L before and during pregnancy are associated with an increased risk of adverse pregnancy outcomes and fetal adverse effects, including increased risk for miscarriage, major birth defects (including microcephaly and major cardiac malformations), intrauterine fetal growth retardation, and future intellectual disability with low IQ *(see Data).* To reduce the risk of hyperphenylalaninemia-induced fetal adverse effects, blood phenylalanine concentrations should be maintained between 120 and 360 micromol/L during pregnancy and during the 3 months before conception *[see Dosage and Administration (2.4)].*

Dose Adjustments During Pregnancy and the Postpartum Period

Phenylalanine concentrations below 30 micromol/L in pregnant women with PKU treated with PALYNZIQ may be associated with adverse fetal outcomes.

- Monitor blood phenylalanine concentrations during pregnancy.
- Adjust the dosage of PALYNZIQ or modify dietary protein and phenylalanine intake to avoid blood phenylalanine concentrations below 30 micromol/L *[see Dosage and Administration (2.4)].*

Data

Human Data

Uncontrolled Maternal PKU: Available data from the Maternal Phenylketonuria Collaborative Study on 468 pregnancies and 331 live births in pregnant women with PKU demonstrated that uncontrolled phenylalanine concentrations above 600 micromol/L are associated with an increased risk for miscarriage, major birth defects (including microcephaly and major cardiac malformations), intrauterine fetal growth retardation, and future intellectual disability with low IQ.

Animal Data
All developmental toxicity studies were conducted in animals (rats and rabbits) without PKU, in which treatment with pegvaliase-pqpz produced a dose-dependent reduction in maternal blood phenylalanine concentrations. At doses that produced maternal toxicity and/or effects on embryo-fetal development, the maternal plasma phenylalanine concentrations were markedly reduced compared to the control group. The contribution of maternal phenylalanine depletion to the incidence of embryo-fetal developmental effects was not evaluated.

Subcutaneous administration of 5 mg/kg/day pegvaliase-pqpz (5 times the maximum recommended daily dose based on bodyweight [mg/kg]) in pregnant rabbits during the period of organogenesis produced embryo-lethality (increased resorptions), marked reduction in fetal weight, and fetal malformations. The malformations included multiple external abnormalities of the head, body and limbs, multiple soft tissue malformations (reduced size or absence of kidneys, diaphragmatic hernia, corneal opacity, discoloration or reduced size of eyes, and reduced size of lungs) and multiple skeletal malformations of the craniofacial bones, vertebrae, sternebrae, ribs, pelvis, limbs, and digits. An increase in variations and delayed ossification was also observed in all skeletal regions. The adverse developmental effects were associated with maternal toxicity, as indicated by marked impairment of weight gain and food consumption. Deaths associated with weight loss and abortion occurred in 8% of the pregnant rabbits treated with 5 mg/kg/day pegvaliase-pqpz.

Subcutaneous administration of 2 mg/kg/day pegvaliase-pqpz (2 times the maximum recommended daily dose based on bodyweight [mg/kg]) in pregnant rabbits had no adverse effects on embryo-fetal development. Systemic exposure to pegvaliase-pqpz was detected in fetuses from rabbits treated with 2 or 5 mg/kg/day.

Pegvaliase-pqpz increased fetal alterations when administered daily in pregnant rats at doses of 8 mg/kg subcutaneously and higher (2.8 times the human steady-state area under the curve [AUC] at the maximum recommended daily dose) during a 28-day premating period, mating, and through the period of organogenesis. The fetal alterations were limited to skeletal variations such as cervical ribs, bifid centra of lumbar and thoracic vertebrae, and incomplete ossification of squamosal bones, frontal bones, lumbar vertebra arch, and ribs. Daily administration of 20 mg/kg subcutaneously (13 times the human steady-state AUC at the recommended maximum daily dose) to pregnant rats produced reductions in litter sizes and fetal weights, which was associated with maternal toxicity (decreased body weight, ovarian weight, and food consumption). The decrease in litter sizes at 20 mg/kg subcutaneously was secondary to reductions in corpora lutea and implantations. Systemic exposure to pegvaliase-pqpz was detected in fetuses from rats treated with 20 mg/kg of pegvaliase-pqpz (13 times the human steady-state AUC at the recommended maximum daily dose). Subcutaneous administration of 2 mg/kg/day pegvaliase-pqpz (less than the human steady state AUC at the maximum recommended daily dose) in pregnant rats had no adverse effects on embryo-fetal development.

Pegvaliase-pqpz decreased pup weight, litter size, and survival of offspring during lactation, and delayed sexual maturation of offspring when administered daily in rats at 20 mg/kg subcutaneously (13 times the human steady-state AUC at the recommended maximum daily dose), with dosing starting before mating and continuing through lactation. The effects in offspring were associated with maternal toxicity. No effects in offspring were observed at 8 mg/kg/day subcutaneously (2.8 times the human steady-state AUC at the recommended maximum daily dose). A follow-up study of the same design evaluated additional parameters of physical and neurobehavioral development in offsprings; No effects of pegvaliase-pqpz were noted at the maternal NOAEL dose of 8 mg/kg/day.

8.2 Lactation

Risk Summary

There are no data on the presence of pegvaliase-pqpz in human milk, the effects on the breastfed infant, or the effects on milk production. A pre-/post-natal study in rats showed that pegvaliase-pqpz is present in rat milk and that administration of pegvaliase-pqpz during lactation decreased pup weight and survival *[see Use in Specific Populations (8.1)]*. However, systemic absorption of pegvaliase-pqpz was not detected in the rat pups. PALYNZIQ may cause low phenylalanine concentrations in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PALYNZIQ and any potential adverse effects on the breastfed infant from PALYNZIQ or from the underlying condition *(see Clinical Considerations)*.

Clinical Considerations

Monitor blood phenylalanine concentrations in breastfeeding women treated with PALYNZIQ.

8.4 Pediatric Use

The safety and effectiveness of PALYNZIQ to reduce blood phenylalanine concentrations have been established in pediatric patients 12 years and older with PKU who have uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on existing management. Use of PALYNZIQ for this indication is supported by evidence from Study 4, an open label randomized 2-arm study in patients who are 12 to less than 18 years of age *[see Clinical Pharmacology (12) and Clinical studies (14)]*.

In Study 4, 16 out of 36 (44%) pegvaliase-treated patients experienced eosinophilia. Incidence of eosinophil levels higher than upper limit of normal was more frequent during the induction/titration phase and decreased during the maintenance phase *[see Adverse Reactions (6.1)]*.

The safety and effectiveness of PALYNZIQ in pediatric patients younger than 12 years of age have not been established.

8.5 Geriatric Use

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

11 DESCRIPTION

Pegvaliase-pqpz is a phenylalanine-metabolizing enzyme that is composed of recombinant phenylalanine ammonia lyase (rAvPAL) conjugated to N-hydroxysuccinimide (NHS)-methoxypolyethylene glycol (PEG). rAvPAL is manufactured in *Escherichia coli* bacteria transformed with a plasmid containing the phenylalanine ammonia lyase (PAL) gene derived from *Anabaena variabilis*. During the rAvPAL manufacturing process, fermentation is carried out in nutrient medium containing the antibiotic kanamycin. However, kanamycin is cleared in the manufacturing process and is not detectable in the final product. rAvPAL is a homotetrameric protein with a molecular weight of 62 kD per monomer. To produce pegvaliase-pqpz, an average of nine (9) 20 kD PEG molecules are covalently bound (or conjugated) to each monomer of rAvPAL. The total molecular weight of pegvaliase-pqpz (rAvPAL-PEG) is approximately 1000 kD.

PALYNZIQ (pegvaliase-pqpz) injection, intended for subcutaneous injection, is a clear to slightly opalescent, colorless to pale yellow, sterile, preservative-free solution and is formulated at pH 6.6 to 7.4.

PALYNZIQ is provided in a single-dose prefilled syringe and is available in three dosage strengths: 2.5 mg/0.5 mL, 10 mg/0.5 mL, and 20 mg/mL. PALYNZIQ contents for each dosage strength are summarized in Table 5.

Table 5: Contents of PALYNZIQ

Strength	Total Contents per Prefilled Syringe
PALYNZIQ 2.5 mg/0.5 mL prefilled syringe	2.5 mg pegvaliase-pqpz (expressed as the amount of rAvPAL conjugated to 7.25 mg of 20 kD PEG in 0.5 mL Water for Injection, USP) and contains the following inactive ingredients: sodium chloride (for tonicity adjustment), *trans*-cinnamic acid (0.07 mg), and tromethamine and tromethamine hydrochloride (for pH adjustment).
PALYNZIQ 10 mg/0.5 mL prefilled syringe	10 mg pegvaliase-pqpz (expressed as the amount of rAvPAL conjugated to 29 mg of 20 kD PEG in 0.5 mL Water for Injection, USP) and contains the following inactive ingredients: sodium chloride (for tonicity adjustment), *trans*-cinnamic acid (0.07 mg), and tromethamine and tromethamine hydrochloride (for pH adjustment).
PALYNZIQ 20 mg/mL prefilled syringe	20 mg pegvaliase-pqpz (expressed as the amount of rAvPAL conjugated to 58 mg of 20 kD PEG in 1 mL Water for Injection, USP) and contains the following inactive ingredients: sodium chloride (for tonicity adjustment), *trans*-cinnamic acid (0.15 mg), and tromethamine and tromethamine hydrochloride (for pH adjustment).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pegvaliase-pqpz is a PEGylated phenylalanine ammonia lyase (PAL) enzyme that converts phenylalanine to ammonia and *trans*-cinnamic acid. It substitutes for the deficient phenylalanine hydroxylase (PAH) enzyme activity in patients with PKU and reduces blood phenylalanine concentrations.

12.2 Pharmacodynamics

PALYNZIQ treatment of adult patients with PKU resulted in the reduction of blood phenylalanine concentrations from pre-treatment baseline *[see Clinical Studies (14)]*. The reduction of blood phenylalanine concentrations diminished with decreased pegvaliase-pqpz plasma concentrations.

PALYNZIQ treatment of patients with PKU resulted in increased ammonia and *trans*-cinnamic acid concentrations from pre-treatment baseline. The time course of ammonia and *trans*-cinnamic acid concentrations and the exposure-response relationships for the safety of ammonia and *trans*-cinnamic acid have not been well-characterized in patients with PKU.

12.3 Pharmacokinetics

The pharmacokinetics of pegvaliase-pqpz exhibit high inter-patient and intra-patient variability due to the heterogeneity of the immune response in adult patients with PKU. Higher antibody titers correlated with higher apparent clearance of pegvaliase-pqpz. In the first eight weeks of induction/titration treatment, plasma pegvaliase-pqpz concentrations were low to not measurable. At steady state during maintenance treatment with PALYNZIQ 20 mg, 40 mg, and 60 mg subcutaneously once daily, the mean ± SD (range) plasma trough pegvaliase-pqpz concentrations were: 11.2 ± 9 (0.21 to 29.6) mg/L, 10.4 ± 12.7 (0.18 to 43.1) mg/L and 4.8 ± 10.7 (0 to 39.7) mg/L, respectively. The following pharmacokinetic

parameters were observed in adult patients with PKU treated with PALYNZIQ at maintenance dosages of 20 mg once daily and 40 mg once daily.

Absorption
The median T_{max} was approximately 8 hours. The mean ± SD (range) peak concentration (C_{max}) at steady state was: 14 ± 16.3 (0.26 to 68.5) mg/L and 16.7 ± 19.5 (0.24 to 63.8) mg/L, respectively.

Distribution
The mean ± SD (range) apparent volume of distribution was 26.4 ± 64.8 (1.8 to 241) L and 22.2 ± 19.7 (3.1 to 49.5) L, respectively.

Elimination
The mean ± SD (range) apparent clearance at steady state was 0.39 ± 0.87 (0.018 to 3.66) L/h and 1.25 ± 2.46 (0.034 to 8.88) L/h, respectively. The mean ± SD (range) half-life was 47 ± 42 (14 to 132) hours and 60 ± 45 (14 to 127) hours, respectively.

Metabolism
The metabolism of phenylalanine ammonia lyase is expected to occur via catabolic pathways and be degraded into small peptides and amino acids.

Excretion
The route of elimination of pegvaliase-pqpz has not been studied in humans.

Special Populations
In patients who are 12 to less than 18 years of age in Study 4, the mean ± SD (range) plasma peak concentration (C_{max}) at steady state during maintenance treatment with PALYNZIQ 20 mg, 40 mg, and 60 mg subcutaneously once daily was: 2.33 mg/L (n=1), 2.48 ± 3.81 (0.038 to 12.5) mg/L, and 1.75 ± 2.2 (0.074 to 6.01) mg/L, respectively.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described below with the incidence of ADA in other studies, including those of pegvaliase-pqpz or of other pegvaliase products.

Anti-Drug Antibodies
In Studies 1, 2, and 3 (clinical trials of PALYNZIQ with induction/titration/maintenance dosage regimen), 100% of PALYNZIQ-treated patients developed anti-pegvaliase-pqpz antibodies, including 91% (N = 235/258) of patients who developed anti-pegvaliase-pqpz antibodies by Week 4 of treatment. Mean anti-pegvaliase-pqpz antibody titers peaked 2 weeks after PALYNZIQ initiation and remained elevated throughout treatment (greater than 3 years after treatment initiation).

Anti-Phenylalanine Ammonia Lyase Antibodies
- Anti-phenylalanine ammonia lyase (PAL) IgM antibodies were detected in 98% (265/270) of PALYNZIQ-treated patients by 2 months after treatment initiation, with incidence declining over time to 67% of patients (114/171) at 36 months.
- Anti-PAL IgG antibodies were detected in 99.6% (226/227) of PALYNZIQ-treated patients by 4 months after treatment initiation.

- Mean anti-PAL IgM and IgG titers peaked at approximately 3 and 6 months, respectively, after treatment initiation and remained elevated throughout treatment (greater than 3 years after treatment initiation).

Anti-PEG Antibodies

- Drug-induced anti-PEG IgM antibodies were detected in 98% (277/284) of PALYNZIQ-treated patients.
- Drug-induced anti-PEG IgG antibodies were detected in 98% (278/284) of PALYNZIQ-treated patients.
- Mean anti-PEG IgM and IgG titers peaked at 1 to 3 months after treatment initiation *[see Drug Interactions (7.1)]*.

In Study 4, 100% of PALYNZIQ-treated patients who were 12 to less than 18 years of age developed anti-pegvaliase-pqpz antibodies, anti-PAL IgG and IgM, anti-PEG IgG and IgM. The overall time course of anti-drug antibody development in these patients was similar to that in adult patients; however, the anti-pegvaliase-pqpz antibody titers were generally higher in patients who were 12 to less than 18 years of age compared to those in adult patients with PKU.

Neutralizing Antibodies

Neutralizing antibodies (NAb) capable of inhibiting PAL enzyme activity were detected on at least one measurement in 89% (253/284) of PALYNZIQ-treated patients over time in Studies 1, 2 and 3. Mean NAb titers peaked and reached a plateau at 16 to 20 weeks of treatment and then remained present throughout treatment (greater than 3 years after treatment initiation). In Study 4, 100% of PALYNZIQ-treated patients who were 12 to less than 18 years of age developed NAb with a similar time course to that in adult patients.

IgE Antibodies

In Studies 1, 2, and 3, twenty-seven of 29 PALYNZIQ-treated patients who had anaphylaxis were tested for anti-pegvaliase-pqpz IgE antibodies which recognize the PEGylated protein product. Of the 27 patients tested for anti-pegvaliase-pqpz IgE antibodies, 26 patients tested negative. The one patient who tested positive for anti-pegvaliase-pqpz- IgE antibodies on the screening test did not have sufficient sample to confirm IgE positivity. This patient tested negative for anti-pegvaliase-pqpz- IgE at routine visits prior to and after the anaphylaxis episode (not at times of anaphylaxis) *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

In Study 4, of the four PALYNZIQ-treated patients who were 12 to less than 18 years of age that experienced anaphylaxis, three were tested and all were negative for pegvaliase-specific IgE antibodies *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

Sixty-seven of 285 PALYNZIQ-treated patients in Studies 1, 2 and 3 were tested for both anti-PAL IgE antibodies, which recognize the recombinant PAL protein, and for anti-pegvaliase-pqpz IgE antibodies during routine study visits (not at times of anaphylaxis episodes) or during additional visits for hypersensitivity reactions. Of those 67 patients, 5 (8%) tested positive at least once for anti-PAL IgE antibodies but negative for anti-pegvaliase-pqpz-IgE antibodies.

Circulating Immune Complexes

In Studies 1, 2, and 3, the highest frequency of hypersensitivity reactions (consistent with a Type III immune complex-mediated hypersensitivity mechanism) occurred within the first 6 months of PALYNZIQ treatment when the mean circulating immune complex (CIC) concentrations were at their highest and mean complement C3 and C4 concentrations were at their lowest *[see Warnings and Precautions (5.3) and Adverse Reactions (6.1)]*.

- Mean CIC concentrations decreased and complement levels increased over time as the exposure-adjusted rate of hypersensitivity reactions decreased.
- At 12 weeks of treatment, IgG CIC and IgM CIC concentrations were above the upper limit of normal in 63% (164/259) and 42% (109/259) of PALYNZIQ-treated patients, respectively, and returned towards baseline 3 years after treatment initiation.
- At 6 months after treatment initiation, 61% (110/180) of PALYNZIQ-treated patients had complement C3 concentrations less than lower limit of normal (LLN). At 3 months after treatment initiation, 38% (94/248) of PALYNZIQ-treated patients had complement C4 concentrations less than LLN.
- At 36 months after treatment initiation, the incidence of low complement C3 and C4 concentrations decreased over time, but approximately 35% (34/96) and 12% (11/96) of PALYNZIQ-treated patients had low C3 and C4 concentrations, respectively.

Anti-Drug Antibody Effects on Pharmacokinetics and Efficacy
Higher antibody responses for all antibody analytes, including NAb, were associated with lower mean trough pegvaliase-pqpz concentrations and with higher blood phenylalanine concentrations.

Anti-Drug Antibody Effects on Safety
Hypersensitivity reactions generally occurred more frequently in PALYNZIQ-treated patients with higher antibody titers. PALYNZIQ-treated patients with higher mean change in IgG CIC concentrations from pre-treatment baseline tended to have higher discontinuation rates than those with lower mean change in IgG CIC concentrations.

The effect of ADAs on safety of PALYNZIQ in pediatric patients 12 years of age and older with PKU has not been fully characterized.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity and genotoxicity studies have not been performed with pegvaliase-pqpz. Based on its mechanism of action, pegvaliase-pqpz is not expected to be tumorigenic.

Pegvaliase-pqpz produced impaired fertility in female rats at 20 mg/kg/day subcutaneously (13 times the human steady-state AUC at the maximum recommended daily dose), as indicated by decreases in corpora lutea, implantations, and litter size. These effects were associated with maternal toxicity (decreased body weight, ovarian weight, and food consumption). No effects on mating or fertility were observed in female rats with 8 mg/kg/day subcutaneously (2.8 times the human steady-state AUC at the maximum recommended daily dose) or in male rats with 20 mg/kg/day subcutaneously.

13.2 Animal Toxicology and/or Pharmacology

In rats without PKU treated with pegvaliase-pqpz, dose-dependent vacuolation in multiple organs and tissues was observed in the 4- and 26-week repeat dose toxicity studies at doses of 8 mg/kg subcutaneously or greater administered twice weekly (less than the human steady state AUC at the maximum recommended daily dose). Vacuolation occurred in renal tubule cells and in histiocytic cells of the liver, spleen, testes, adrenal cortex, mesenteric lymph node, and mandibular lymph node. Vacuolation in histiocytes of the affected organs and tissues persisted after cessation of treatment. The vacuolation observed in these studies was not associated with organ-related toxicities as determined by clinical

chemistry/urinalysis and histopathological examination. The clinical significance of these findings and functional consequences are unknown.

In the 39-week repeat dose toxicity study in monkeys, pegvaliase-pqpz 3 mg/kg subcutaneously twice weekly (2 times the human steady state AUC at the maximum recommended daily dose) produced systemic arteritis involving small arteries and arterioles in a wide range of organs and tissues (kidney, urinary bladder, pancreas, gallbladder, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, lung, heart, sciatic nerve, lacrimal gland, mandibular lymph node, epididymis, seminal vesicle, ovary, uterus, cervix, and vagina) and in subcutaneous injection sites. Arteritis was likely due to the immune-mediated response (e.g., immune complex deposition in blood vessels) associated with chronic administration of a foreign protein to the animals. The incidence and severity of systemic arteritis was dose-dependent. The vascular inflammation observed in this study was not associated with organ related toxicities as determined by clinical pathology parameters (hematology, clinical chemistry, and urinalysis) and histopathological examination.

Studies of longer duration in rats and monkeys treated with pegvaliase-pqpz have not been conducted.

14 CLINICAL STUDIES

Study 2: Induction/Titration/Maintenance Treatment

Study 2 (NCT01819727) was an open-label, randomized, multi-center study of adults with PKU to assess safety and tolerability of self-administered PALYNZIQ in 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 protein and phenylalanine intake, and/or prior treatment with sapropterin dihydrochloride. Patients previously treated with sapropterin dihydrochloride were required to discontinue use at least 14 days prior to the first dose.

The 261 enrolled patients were aged 16 to 55 years (mean: 29 years) and had a baseline mean (range) blood phenylalanine of 1,233 (285, 2330) micromol/L. One hundred forty nine out of 261 (57%) patients were taking medical food at baseline and 41 out of 261 patients (16%) were on a Phe-restricted diet at baseline (defined as receiving greater than 75% of total protein intake from medical food). 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 2, 54 (21%) patients discontinued treatment during Study 2, 4 patients completed Study 2 and did not continue to Study 3 (referred to as Study 302, NCT01889862), 152 patients continued to the eligibility period of Study 3, and 51 patients continued directly from Study 2 into the long-term treatment period of Study 3.

Study 3: Efficacy Assessment

A total of 164 adult patients with PKU who were previously treated with PALYNZIQ (152 patients from Study 2 and 12 patients from other PALYNZIQ trials) enrolled in Study 3 and continued treatment with PALYNZIQ in Study 3 for up to 13 weeks to assess eligibility for randomized withdrawal period.

Randomized Withdrawal Period

Following this period of up to 13 weeks of additional PALYNZIQ treatment in Study 3, 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 in least squares (LS) mean change in blood phenylalanine concentration from the Study 3 randomized withdrawal baseline to randomized withdrawal Week 8 for each randomized study arm is shown in Table 6. Mean blood phenylalanine concentrations at pre-treatment baseline (Study 2 or other PALYNZIQ trials) are also shown in Table 6. At Study 3 randomized withdrawal Week 8, PALYNZIQ-treated patients (20 mg once daily or 40 mg once daily) maintained their blood phenylalanine concentrations as compared to their randomized withdrawal baseline, whereas patients randomized to matching placebo (20 mg once daily or 40 mg once daily) returned to their pretreatment baseline blood phenylalanine concentrations (Figure 1).

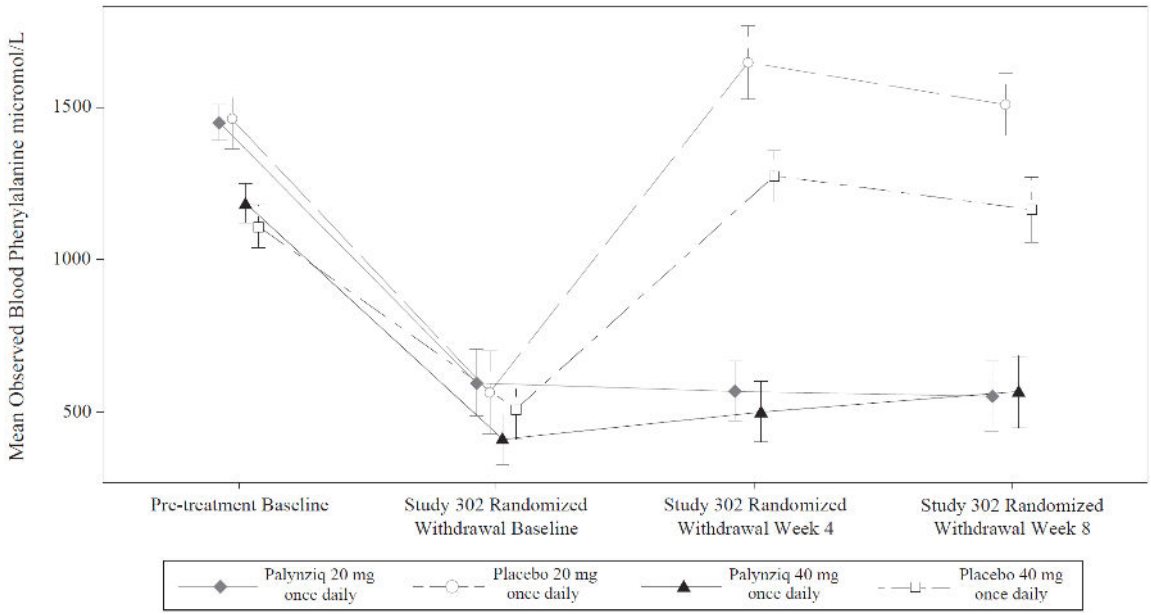
Table 6: Primary Endpoint: LS Mean Change in Blood Phenylalanine Concentration from Randomized Withdrawal Baseline to Week 8 in Adult Patients with PKU – Efficacy Assessment in Study 3

Randomized Study Arm	Blood Phenylalanine Concentration (micromol/L) Mean (SD)			LS Mean Change from Study 3 Randomized Withdrawal Baseline to Week 8 (95% CI)	Treatment Difference in LS Mean Change (95% CI) P-value[1]
	Pre-treatment Baseline	Study 3 Randomized Withdrawal Baseline	Study 3 Randomized Withdrawal Week 8		
PALYNZIQ 20 mg once daily	1450.2 (310.5) n = 29	596.8 (582.8) n = 29	553 (582.4) n = 26[2]	-23.3 (-156.2, 109.7)	-973 (-1204.2, -741.9) p < 0.0001
Placebo 20 mg once daily	1459.1 (354.7) n = 14	563.9 (504.6) n = 14	1509 (372.6) n = 13[2]	949.8 (760.4, 1139.1)	
PALYNZIQ 40 mg once daily	1185.8 (344.0) n = 29	410.9 (440.0) n = 29	566.3 (567.5) n = 23[2]	76.3 (-60.2, 212.8)	-588.5 (-830.1, -346.9) p < 0.0001
Placebo 40 mg once daily	1108.9 (266.8) n = 14	508.2 (363.7) n = 14	1164.4 (343.3) n = 10[2]	664.8 (465.5, 864.1)	

[1] Based on the mixed model repeated measures (MMRM) method, with treatment arm, visit, and treatment arm-by-visit interaction as factors adjusting for baseline blood phenylalanine concentration.

[2] Patients who did not complete phenylalanine assessment within the window for Week 8 (Day 43 to 56) were excluded.

Figure 1: Observed Mean (SE) Blood Phenylalanine Concentrations Over 8 Weeks in Adult Patients with PKU in Study 3



Studies 2 and 3 Continuous Treatment

Of 118 patients from Study 2 with a pre-treatment baseline blood phenylalanine concentration greater than 600 micromol/L who were randomized to and received at least one dose of 20 mg once daily PALYNZIQ, 107 patients, 97 patients, 93 patients, 86 patients, and 77 patients were treated for at least 6 months, 12 months, 18 months, 24 months, and 36 months, respectively. During the continuous treatment period, patients were allowed to dose up to 60 mg once daily based on investigator discretion to achieve blood phenylalanine lowering (for example, to achieve blood phenylalanine concentrations between 120 and 360 micromol/L).

Of the 118 patients, a majority (91 patients, 77%) reached their first response, defined as a blood phenylalanine concentration less than or equal to 600 micromol/L, at a time point prior to 36 months. Of the 91 patients, 9 patients (10%) achieved their first response at a dose less than 20 mg once daily, 44 patients (48%) achieved their first response at a dose of 20 mg once daily, 26 patients (29%) achieved their first response at a dose of 40 mg once daily, and 12 patients (13%) achieved their first response at a dose of 60 mg once daily. Of the 44 patients that achieved their first response at a dose of 20 mg once daily, 36 (82%) achieved it by 24 weeks of treatment. Of the 26 patients that achieved their first response at a dose of 40 mg once daily, 18 (69%) achieved it by 16 weeks of treatment. Of the 12 patients that achieved their first response at a dose of 60 mg once daily, 8 (67%) achieved it by 16 weeks of treatment.

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

58 (75%), 51 (66%), and 37 (48%) had a blood phenylalanine concentration less than or equal to 600, 360, and 120 micromol/L, respectively, at 36 months of treatment.

Study 4

Study 4 (NCT05270837) was an open label, randomized, 2-arm study in patients who are 12 to less than 18 years of age who demonstrated inadequate blood phenylalanine control (blood phenylalanine concentration greater than 600 micromol/L) on existing management. Patients were randomized in a 2:1 ratio to receive PALYNZIQ in an induction/titration/maintenance regimen or to continue dietary management for 72 weeks.

Of the 55 randomized patients, 60% were female and 40% were male. The baseline mean (SD) age was 14.4 (1.3) years. The patient population consisted of 87% White, 4% Black, 2% Asian, and 7% not reported. Ethnicity consisted of 4% Hispanic or Latino and 96% not Hispanic or Latino.

Thirty-six patients received PALYNZIQ subcutaneously at doses of 20 mg, 40 mg, or 60 mg per day during maintenance dosing, and 19 patients were included in the diet-only control arm. All patients were required to maintain stable dietary protein intake from medical food and intact food up to week 72. Baseline mean (range) blood phenylalanine was 1,025 (635, 1,555) micromol/L in the PALYNZIQ arm and 1,029 (687, 1414) micromol/L in the diet only arm, respectively. Four patients in the PALYNZIQ arm discontinued from Study 4 up to week 72.

Of the 36 patients enrolled in the PALYNZIQ arm, 34/36 (94%) reached a dose of 20 mg per day (median time to first 20 mg per day dose was 12.1 weeks), 26/36 (72%) reached a dose of 40 mg per day (median time to first 40 mg per day dose was 40 weeks), and 14/36 (39%) reached a dose of 60 mg per day (median time to first 60 mg per day dose was 60.7 weeks).

Patients in the PALYNZIQ arm showed a significant mean reduction from baseline in blood Phe levels at Week 72 compared to patients in the diet only arm (Table 7).

Table 7: Change from Baseline in Blood Phe Level: Randomized Subjects in Study 4

Study Visit	**PALYNZIQ**	**Diet Only**
Baseline	N = 36	N = 19
Mean (SD)	1025 (254)	1029 (199)
Week 72[1]	N = 32	N = 17
Mean (SD)	567 (396)	973 (234)
Mean (SD) Change at Week 72[1]	-473 (285)	-19 (249)
Treatment Difference (95% CI)[2]	-409 (-579, -240)	

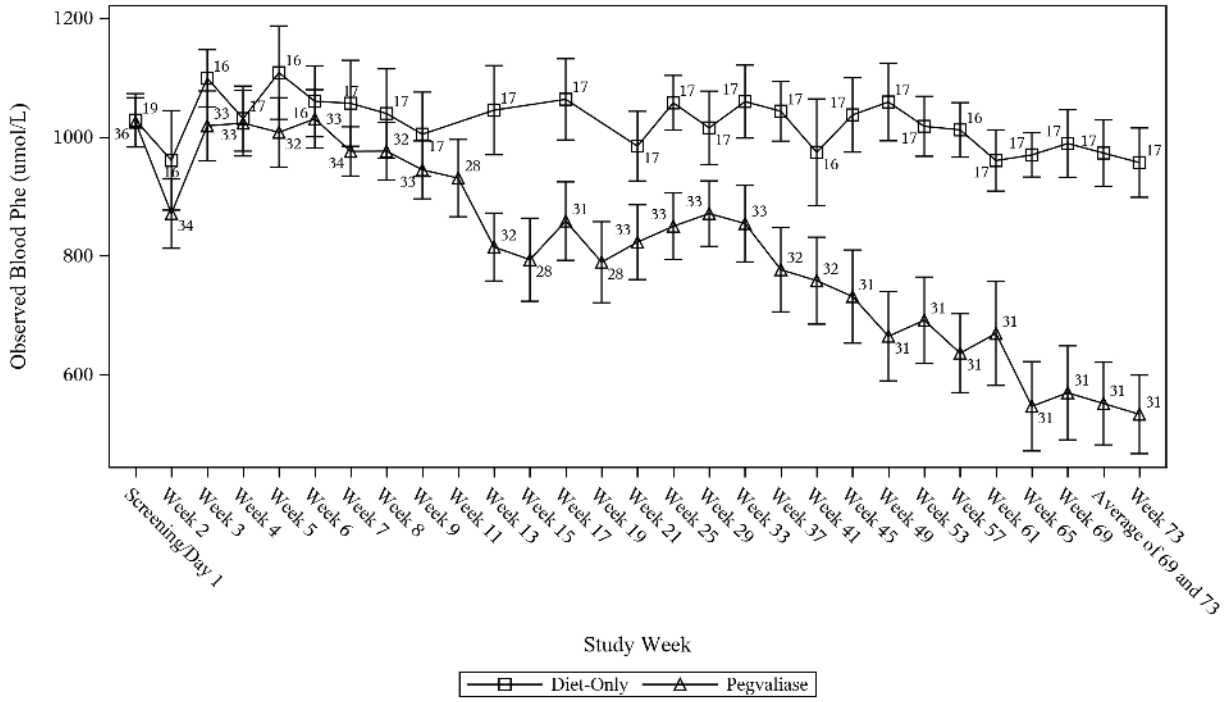
CI, confidence interval; SD, standard deviation.

[1] Calculated as the average of Week 69 and Week 73 based on the observed data.

[2] Missing data was imputed. The treatment difference in the least square (LS) means was calculated using an analysis of covariance model including the randomization strata (baseline blood Phe ≤ 1000 µmol/L or > 1000 µmol/L) as factors and baseline blood Phe as a covariate. P-value for testing the treatment difference in LS means < 0.0001.

Figure 2 shows the blood phenylalanine concentration over time of patients treated with PALYNZIQ patients on diet only.

Figure 2: Mean (SE) Plot of Observed, Change and Percent Change from Baseline in Blood Phenylalanine Over Time in Study 4



16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

PALYNZIQ (pegvaliase-pqpz) injection is supplied as a preservative-free, sterile, clear to slightly opalescent, colorless to pale yellow solution. All dosage strengths of PALYNZIQ are provided in a 1 mL glass syringe with a 26-gauge, 0.5 inch needle.

Each carton contains 1 or 10 trays with single-dose prefilled syringe(s), Prescribing Information, Medication Guide, and Instructions for Use. The following packaging configurations are available.

Table 8: PALYNZIQ Packaging Configurations

Pegvaliase-pqpz 2.5 mg/0.5 mL	1 syringe/carton	NDC 68135-058-90
Pegvaliase-pqpz 10 mg/0.5 mL	1 syringe/carton	NDC 68135-756-20
Pegvaliase-pqpz 20 mg/mL	1 syringe/carton 10 syringes/carton	NDC 68135-673-40 NDC 68135-673-45

Storage and Handling

- Store in refrigerator at 36°F to 46°F (2°C to 8°C) in its original carton to protect from light.
- Do not freeze or shake.

- *For patients*: If needed, store PALYNZIQ in the original carton at room temperature between 68°F to 77°F (20°C to 25°C) for up to 30 days. Record the date removed from refrigeration on the carton. Once stored at room temperature, do not return the product to the refrigerator.
- The shelf-life expires after storage at room temperature for 30 days, or after the expiration date on the product carton, whichever is earlier.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Anaphylaxis and Other Hypersensitivity Reactions

- Advise patients that PALYNZIQ may cause hypersensitivity reactions, including anaphylaxis that can occur at any time. Instruct patients to recognize the signs and symptoms of anaphylaxis *[see Warnings and Precautions (5.1, 5.3)]*.
- Instruct patients to carry epinephrine with them at all times during PALYNZIQ treatment. Instruct the patient and observer (if applicable) on the appropriate use of epinephrine for anaphylaxis *[see Warnings and Precautions (5.1)]*.
- Instruct patients who experience anaphylaxis to seek immediate medical care, discontinue therapy, and resume treatment only at the instruction of a healthcare provider *[see Warnings and Precautions (5.1)]*.

PALYNZIQ REMS Program

PALYNZIQ is available only through a restricted program called the PALYNZIQ REMS *[see Warnings and Precautions (5.2)]*. Inform the patient of the following notable requirements:

- Patients must be enrolled in the PALYNZIQ REMS.
- Patients must 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 fill a prescription for epinephrine and carry it with them at all times.
- Patients will be given a PALYNZIQ Patient Wallet Card that they should carry with them at all times. This card describes symptoms which, if experienced, should prompt the patient and observer (if applicable) to immediately seek medical care. Advise the patient to show the PALYNZIQ Wallet Card to other treating healthcare providers.

PALYNZIQ is available only from certified pharmacies participating in the program. Therefore, provide patients with the telephone number and website for information on how to obtain the product.

Administration

- Advise patients to monitor their dietary protein and phenylalanine intake throughout treatment with PALYNZIQ, and adjust intake as directed by their healthcare provider based on blood phenylalanine concentrations *[see Dosage and Administration (2.4)]*.
- Provide appropriate instruction for methods of self-injection, including careful review of the PALYNZIQ Medication Guide and Instructions for Use. Instruct patients in the use of aseptic technique when administering PALYNZIQ *[see Dosage and Administration (2.5)]*.
- Inform patients that a healthcare provider will show them or their caregiver how to prepare to inject PALYNZIQ before self-administering.
- Advise patients not to inject into moles, scars, birthmarks, bruises, rashes, or areas where the skin is hard, tender, red, damaged, burned, inflamed, or tattooed.
- Advise patients to rotate injection sites with each dose.

- Advise patients that injection site infections may occur and to check the injection site for redness, swelling, or tenderness prior to injection. Instruct patients to contact their healthcare provider if signs or symptoms of an infection develop, persist, or worsen *[see Warnings and Precautions (5.4)]*.
- Advise patients to not administer PALYNZIQ into the affected area until the infection has resolved.
- Advise patients to follow sharps disposal recommendations *[see Instructions for Use]*. Instruct patients on safe disposal procedures.
- Advise patients that the shelf-life expires after storage at room temperature for 30 days or after the expiration date on the product carton, whichever is earlier.

Pregnancy

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

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. Encourage these patients to report their pregnancy to BioMarin (1-866-906-6100) *[see Use in Specific Populations (8.1)]*.

Manufactured by:
BioMarin Pharmaceutical Inc.
Novato, CA 94949
US License No. 1649

Medication Guide
PALYNZIQ® (Pal-lin-zeek)
(pegvaliase-pqpz)
injection, for subcutaneous use

What is the most important information I should know about PALYNZIQ?

PALYNZIQ can cause a severe allergic reaction (anaphylaxis). These reactions may be life-threatening and may happen any time during treatment with PALYNZIQ. Severe allergic reactions are a serious and common side effect of PALYNZIQ.

- You will get your first injection of PALYNZIQ under the supervision of a healthcare provider prepared to manage a severe allergic reaction. You will be closely watched for at least 1 hour after your injection for a severe allergic reaction.
- If you have a severe allergic reaction during treatment with PALYNZIQ, you will need to receive epinephrine and get emergency medical help right away.
- Your healthcare provider will decide if you (or your caregiver) are able to give PALYNZIQ injections, recognize the signs and symptoms of a severe allergic reaction, and use epinephrine and get emergency medical help, if needed.
- Your healthcare provider may ask an adult observer (or your caregiver) to be with you during and for at least 1 hour after each PALYNZIQ injection to watch for signs of a severe allergic reaction. If needed, they should be ready to give you epinephrine and get emergency medical help right away.

Stop PALYNZIQ and get emergency medical care right away if you have any of the following signs or symptoms of a severe allergic reaction during treatment with PALYNZIQ:

- fainting (passing out)
- dizziness or lightheadedness
- sudden confusion
- trouble breathing or wheezing
- chest discomfort or chest tightness
- fast heart rate
- swelling of your face, lips, eyes, or tongue
- throat swelling or tightness
- flushed or red skin
- skin rash, itching, or raised bumps on skin
- nausea, vomiting, or diarrhea
- losing control of urine or stools

- Your healthcare provider will give you a prescription for epinephrine and teach you (or your caregiver) and your observer, if needed, how to use it if you have a severe allergic reaction. **Carry epinephrine with you at all times during treatment with PALYNZIQ.** Read the Patient Information that comes with epinephrine for more information.
- **If you have a severe allergic reaction, stop taking PALYNZIQ** until you talk with your healthcare provider. Tell them that you had a severe allergic reaction. They will decide if it is safe for you to keep using it.
  - Your healthcare provider may prescribe other medicines to take before your PALYNZIQ injection to help reduce the symptoms of an allergic reaction.
  - If your healthcare provider decides you can continue treatment with PALYNZIQ, you will receive your next injection under the supervision of a healthcare provider prepared to manage a severe allergic reaction, where you will be closely watched for at least 1 hour after your injection for signs of a severe allergic reaction.
- **Your healthcare provider will give you a PALYNZIQ Patient Wallet Card** that lists the signs and symptoms of a severe allergic reaction. You (or your caregiver), or your observer, should get emergency medical help right away if any of these signs or symptoms occur. **Carry this card with you at all times during treatment with PALYNZIQ.** Show this card to any other healthcare provider who treats you.

PALYNZIQ is only available through a restricted program called the PALYNZIQ Risk Evaluation and Mitigation Strategy (REMS). Before you can receive PALYNZIQ, you must:

- enroll in the program.
- learn about the risk of a severe allergic reaction (anaphylaxis) from a healthcare provider certified in the PALYNZIQ REMS so you can understand the risks and benefits of treatment with PALYNZIQ.
- fill a prescription for epinephrine and carry it with you at all times during treatment with PALYNZIQ.
- carry the PALYNZIQ Patient Wallet Card with you at all times.

See **"What are the possible side effects of PALYNZIQ?"** for more information about side effects.

What is PALYNZIQ?

PALYNZIQ is a prescription medicine used to reduce blood levels of phenylalanine in adults and children 12 years of age and older with phenylketonuria (PKU) who have uncontrolled blood phenylalanine levels greater than 600 micromol/L on their current treatment.

It is not known if PALYNZIQ is safe and effective in children younger than 12 years of age.

Before injecting PALYNZIQ, tell your healthcare provider about all of your medical conditions, including if you:

- cannot or do not want to use epinephrine to treat a severe allergic reaction.
- are pregnant or plan to become pregnant. It is not known if PALYNZIQ will harm your unborn baby. Tell your healthcare provider right away if you become pregnant or think you might be pregnant during treatment with PALYNZIQ.
  - If your phenylalanine levels are too high or too low during pregnancy, this may affect your unborn baby. You and your healthcare provider can decide the best way for you to manage your blood phenylalanine levels and if taking PALYNZIQ is right for you and your unborn baby.
  - It is very important to keep your phenylalanine at the levels your healthcare provider recommends during pregnancy.

- **Pregnancy Surveillance Program.** There is a pregnancy surveillance program for females who take PALYNZIQ during pregnancy, or who become pregnant during treatment with PALYNZIQ or within 1 month after their last dose of PALYNZIQ. This program collects information about the health of you and your baby during treatment with PALYNZIQ. Talk to your healthcare provider about how you can take part in this program or call BioMarin at 1-866-906-6100.
- are breastfeeding or plan to breastfeed. It is not known if PALYNZIQ passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with PALYNZIQ.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, or herbal supplements.

How should I take PALYNZIQ?

- Your healthcare provider will give you the PALYNZIQ injection until they decide that you (or your caregiver) can give it. See **"What is the most important information I should know about PALYNZIQ?"**
- Your healthcare provider may prescribe medicines for you to take before your PALYNZIQ injection to help reduce the symptoms of an allergic reaction.
- If your healthcare provider decides that you (or your caregiver) can give your PALYNZIQ injections, your healthcare provider will show you (or your caregiver) how to prepare and give the injections. **See the detailed "Instructions for Use" that comes with PALYNZIQ for information about how to prepare and inject a dose of PALYNZIQ**.
- Use PALYNZIQ exactly as your healthcare provider tells you to, including how much to inject and when to inject it.
- PALYNZIQ comes in prefilled syringes with 3 different strengths (2.5 mg, 10 mg, or 20 mg). You may need more than 1 prefilled syringe for your prescribed dose.
- Monitor the amount of protein and phenylalanine you eat or drink during treatment with PALYNZIQ. Your healthcare provider may change your diet based on the amount of phenylalanine in your blood. Follow your healthcare provider's instructions about the amount of protein and phenylalanine you should have in your diet.
- If you miss a dose, take the next dose at the regular time. Do not take 2 doses of PALYNZIQ to make up for a missed dose.

What are the possible side effects of PALYNZIQ?

PALYNZIQ may cause serious side effects, including:

- **Severe allergic reactions (anaphylaxis).** See **"What is the most important information I should know about PALYNZIQ?"**
- **Other allergic reactions to PALYNZIQ** can happen during treatment. **Call your healthcare provider right away if you get any of the following symptoms of an allergic reaction including**: rash, itching, or swelling of the face, lips, eyes, or tongue. Your healthcare provider may change your dose or temporarily stop treatment with PALYNZIQ, or give you medicine for you to take before your PALYNZIQ injection to help reduce the symptoms of an allergic reaction.
- **Injection site infections.** Serious infections at the injection site have happened in people during treatment with PALYNZIQ. Some of these injection site infections required hospitalization, surgery, treatment with antibiotics given through the vein, or stopping treatment with PALYNZIQ. Change (rotate) your injection site and check your injection site for redness, swelling, or tenderness before each injection. Tell your healthcare provider right away if you develop signs or symptoms of an infection at your injection site that are new, do not go away, or get worse, including:
  - pain, redness, swelling, or tenderness
  - the area feels hard
  - fluid or pus
  - blisters
  - a dark scab
  - an open wound

  Do not inject PALYNZIQ into the affected area until the infection has cleared.
- **Low levels of phenylalanine in your blood (hypophenylalaninemia).** Your healthcare provider will monitor your blood levels of phenylalanine during treatment with PALYNZIQ.

The most common side effects of PALYNZIQ include:

- injection site reactions: redness, itching, pain, bruising, rash, swelling, tenderness
- joint pain
- allergic reactions
- headache
- skin reactions that spread and last at least 14 days, such as itching, rash, redness
- nausea
- stomach pain
- vomiting
- cough
- mouth and throat pain
- itching
- diarrhea
- stuffy nose
- feel very tired
- dizziness
- anxiety

The most common side effects of PALYNZIQ in people 12 years to less than 18 years of age include:

- injection site reactions: redness, itching, pain, bruising, rash, swelling, tenderness
- joint pain
- headache
- fever
- allergic reactions
- dizziness
- nausea
- vomiting
- feel very tired
- pain in your arms or legs

These are not all the possible side effects of PALYNZIQ. Call your doctor for medical advice about side effects.
You may report side effects to FDA at 1-800-FDA-1088.

How should I store PALYNZIQ?

- Store PALYNZIQ in the refrigerator at 36°F to 46°F (2°C to 8°C).
- If needed, you can store PALYNZIQ at room temperature between 68°F to 77°F (20°C to 25°C) for up to 30 days.
  - Write the date that you remove PALYNZIQ from the refrigerator on the carton.
  - If stored at room temperature, do not put PALYNZIQ back in the refrigerator.
- **Keep PALYNZIQ in the original carton to protect from light.**
- **Do not** freeze or shake PALYNZIQ.
- Throw away PALYNZIQ if it has been stored at room temperature for more than 30 days, or after the expiration date on the carton, whichever comes first.

Keep PALYNZIQ and all medicines out of the reach of children.

General information about the safe and effective use of PALYNZIQ.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use PALYNZIQ for a condition for which it was not prescribed. Do not give PALYNZIQ to other people, even if they have the same symptoms that you have. It may harm them. For more information, ask your pharmacist or healthcare provider for information about PALYNZIQ that is written for health professionals.

What are the ingredients in PALYNZIQ?

Active ingredients: pegvaliase-pqpz

Inactive ingredients: sodium chloride, *trans*-cinnamic acid, tromethamine, and tromethamine hydrochloride

Manufactured by: BioMarin Pharmaceutical Inc. Novato, CA 94949 US License No. 1649

For more information, go to http://www.PALYNZIQ.com/ or call 1-866-906-6100.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 2/2026