INDICATION

PALYNZIQ® (pegvaliase injection) is indicated to reduce blood phenylalanine concentrations in patients with phenylketonuria (PKU) aged 16 years and older who have inadequate blood phenylalanine control (blood phenylalanine levels >600 mol/L) despite dietary management.

IMPORTANT SAFETY INFORMATION

Serious Warnings and Precautions

Systemic hypersensitivity reactions, including anaphylaxis, have been reported after administration of PALYNZIQ and may occur at any time during treatment.

Administer the initial doses of PALYNZIQ under the supervision of a health professional equipped to manage an acute systemic hypersensitivity (anaphylactic) reaction, and closely observe patients for at least 1 hour following injection.

Prescribe auto-injectable epinephrine. Prior to the first self-administered/caregiver-administered dose of PALYNZIQ, instruct the patient (or caregiver) and a trained observer on appropriate epinephrine use. Instruct the patient to seek immediate medical care in the case of epinephrine use. Instruct patients to carry auto-injectable epinephrine with them at all times during PALYNZIQ treatment.

Discontinue PALYNZIQ in patients who experience a severe systemic hypersensitivity reaction (e.g., severe serum sickness, severe angioedema, or a severe anaphylactic reaction) and in patients who experience a recurrent mild-to-moderate anaphylactic reaction.

PALYNZIQ is contraindicated in patients who have had a severe systemic hypersensitivity reaction (e.g., severe serum sickness, severe angioedema, or a severe anaphylactic reaction), recurrence of a mild-to-moderate anaphylactic reaction to PALYNZIQ or to any ingredient in the formulation, including any nonmedicinal ingredient or component of the container, or in patients who have had an anaphylactic reaction to a product containing polyethylene glycol (PEG) or to another product containing a PEGylated ingredient.

Use of PALYNZIQ during pregnancy may cause fetal harm. PALYNZIQ is not recommended during pregnancy unless the clinical condition of the woman requires treatment with PALYNZIQ and alternative strategies to lower blood phenylalanine have been considered and exhausted or ruled out. Determine pregnancy status before initiating treatment in women of reproductive potential. Counsel patients on the use of contraception during treatment and for 1 month after discontinuation.

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 1 month following the last dose of PALYNZIQ, the health professional should report PALYNZIQ exposure by calling 1-866-906-6100. Educational materials for patients related to risks of fetal developmental toxicity and other pregnancy-related adverse reactions are available at www.biomarin.ca.

There are no data on the presence of PALYNZIQ in human milk, the effects on the breastfed infant, or the effects on milk production. It is not known whether Palynziq is excreted in human milk. A risk to infants cannot be excluded.

Before initiating treatment, blood phenylalanine level must be measured. Monitoring of blood phenylalanine levels once per month is recommended until the maintenance dose of PALYNZIQ is established. After a maintenance dose is established, periodic blood phenylalanine monitoring is recommended to assess blood phenylalanine control. Dietary phenylalanine intake should remain consistent until a maintenance dose is established.

Due to the potential for an acute systemic hypersensitivity (anaphylactic) reaction, premedication prior to each dose is required during induction and titration. Patients should be instructed to premedicate with an H_1-receptor antagonist and an H_2-receptor antagonist, with or without an antipyretic. During maintenance, premedication may be considered for subsequent injections based on patient tolerability to PALYNZIQ.

Hypersensitivity reactions cover a group of terms that comprise acute systemic hypersensitivity (anaphylactic) reaction, other systemic hypersensitivity reactions such as angioedema or serum sickness, and local hypersensitivity reactions such as reactions at the injection site or other skin reactions. Hypersensitivity reactions can occur at any time during treatment with PALYNZIQ. PALYNZIQ may also increase hypersensitivity to other PEGylated injectable medicinal products. Hypersensitivity-related adverse reactions are more frequently reported in the induction and titration phases compared with the maintenance phase.

Hypersensitivity reactions to PALYNZIQ, such as dizziness and syncope, may affect the ability to drive and use machinery. Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Manifestations of acute systemic hypersensitivity (anaphylactic) reactions included a combination of the following acute signs and symptoms: syncope, hypotension, hypoxia, dyspnea, wheezing, chest discomfort/chest tightness, tachycardia, angioedema (swelling of face, lips, eyes, and tongue), flushing, rash, urticaria, pruritus, and gastrointestinal symptoms (vomiting, nausea, and diarrhea). Acute systemic hypersensitivity (anaphylactic) reactions were considered severe based on the presence of cyanosis or oxygen saturation ≤92%, hypotension (systolic blood pressure <90 mm Hg in adults), or syncope. Acute systemic hypersensitivity (anaphylactic) reactions generally occurred within the first hour after injection; however, reactions have occurred up to 24 hours after dosing.

Management of hypersensitivity reactions should be based on the severity of the reaction; in clinical trials, this included dose adjustment, treatment interruption, additional antihistamines, antipyretics, corticosteroids, and/or oxygen. Acute systemic hypersensitivity (anaphylactic) reactions require treatment with epinephrine and immediate medical care. An epinephrine injection device should be prescribed to patients prior to receiving PALYNZIQ. Patients should be instructed to carry an epinephrine injection device with them at all times during PALYNZIQ treatment.

Initial doses of PALYNZIQ should be administered under supervision of a health professional. Before self-administration, patients and a trained observer should be instructed to recognize the signs and symptoms of acute systemic hypersensitivity (anaphylactic) reactions, in the proper emergency use of the epinephrine injection device, and the requirement to seek immediate medical care. An observer must be present for the first 6 months of treatment when the patient is self-injecting and for at least 1 hour after injecting.

Permanently discontinue PALYNZIQ treatment in patients who experience a severe systemic hypersensitivity reaction (e.g., severe serum sickness, severe angioedema, or a severe anaphylactic reaction), and in those who experience a recurrence of a mild-to-moderate acute systemic hypersensitivity (anaphylactic) reaction.

In clinical trials, 132 (46%) patients reported at least 1 episode of hypophenylalaninemia (defined as 2 consecutive blood Phe measurements <30 mol/L). Of these 132 patients, 33 (12%) reported concurrent events of alopecia. Monitoring of phenylalanine level is recommended once per month during PALYNZIQ treatment. In case of hypophenylalaninemia, dietary protein intake should be increased to appropriate levels and then, if needed, the dose of PALYNZIQ should be reduced.

In clinical trials, the majority of patients experienced injection site reactions, arthralgia, and hypersensitivity reactions; event rates were higher during the induction/titration phase compared with the maintenance phase. The most clinically significant hypersensitivity reactions include acute systemic hypersensitivity (anaphylactic) reactions, angioedema, and serum sickness, including reactions that were severe and/or required permanent discontinuation.

In clinical trials, 47% of patients treated with PALYNZIQ experienced skin reactions (not limited to the injection site) lasting at least 14 days. The most common cutaneous reactions (at least 5% of patients) reported were pruritus, rash, erythema, and urticaria. Other reactions reported included skin exfoliation, generalized rash, erythematous rash, maculopapular rash, and pruritic rash.

Injection site reactions were reported in 93% of patients. The most common injection site reactions (occurring in at least 10% of patients) were erythema, bruising, pruritus, pain, swelling, rash, induration, and urticaria.

In clinical trials, 86% of patients experienced episodes consistent with arthralgia (including back pain, musculoskeletal pain, pain in extremity, and neck pain). Arthralgia occurred as early as the first dose and may occur at any time during treatment.

Severe arthralgia (pain limiting self-care and activities of daily living) was experienced in 5% of patients. Arthralgia episodes were managed with medications (e.g., nonsteroidal anti-inflammatory drugs, glucocorticoids, and/or antipyretics), dose reduction, treatment interruption, or treatment withdrawal.

As with all therapeutic proteins, there is potential for immunogenicity. All patients treated with Palynziq developed a sustained total anti-drug antibody (TAb) response. However, the level of antibody titer was not predictive of hypersensitivity reactions.

The data to support the efficacy and safety of PALYNZIQ in pediatric patients 16 to <18 years of age are limited. The warnings and precautions for PALYNZIQ applicable to adult patients also apply to patients 16 to <18 years of age. No data are available from clinical trials in patients >56 years of age. Efficacy and safety of PALYNZIQ have not been established in patients with hepatic or renal impairment.

Reporting suspected side effects: You can report any suspected adverse reactions associated with the use of health products to Health Canada by any of the following ways:

- **Contact BioMarin Pharmaceutical Inc. at 1-866-906-6100 or email drugsafety@bmrn.com**
- **Report online to Health Canada at https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html or call toll-free 1-866-234-2345**

Please see full Product Monograph available at www.biomarin.ca.