Important information for healthcare professionals for the safe use of PALYNZIQ®▼ (pegvaliase)

▼*This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.*

Hypersensitivity reactions including acute systemic hypersensitivity reactions can occur at any time during PALYNZIQ® treatment. Please read the following information carefully before prescribing PALYNZIQ® to your patient and refer to the *Summary of Product Characteristics* for further information.

Please provide the *Important Information for Patients for the safe use of PALYNZIQ®*, the *PALYNZIQ® Patient alert card and the package leaflet* to all patients.

Please report any suspected adverse reactions (including but not limited to hypersensitivity) to **drugsafety@bmrn.com** or Fax: +1-415-532-3144 or Phone: +1-415-506-6179.

Suspected Adverse Drug Reactions (side effects) or medication errors may be reported using the Medicines Authority ADR reporting form, which is available online at http://www.medicinesauthority.gov.mt/adrportal, and sent by post or email to:
P: Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000
E: postlicensing.medicinesauthority@gov.mt

Indication for use

PALYNZIQ® is indicated for the treatment of patients with phenylketonuria (PKU) aged 16 years and older who have inadequate blood phenylalanine control (blood phenylalanine levels >600 µmol/L) despite prior management with available treatment options.

The safety and efficacy of PALYNZIQ® in children and adolescents from birth to less than 16 years have not been established.

Acute systemic hypersensitivity – the clinical data

- Hypersensitivity reactions, including acute systemic hypersensitivity reactions, angioedema, and serum sickness, have been reported in patients treated with PALYNZIQ® and can occur at any time during treatment. PALYNZIQ® may also increase hypersensitivity to other PEGylated injectable medicinal products
- In clinical trials, 16 out of 285 (6%) patients experienced 25 acute systemic hypersensitivity reactions of any severity based on acute onset of skin and/or mucosal tissue manifestations and at least either respiratory compromise or reduced blood pressure (or associated symptoms of end organ dysfunction)

- Manifestations included a combination of the following acute signs and symptoms: syncope, hypotension, hypoxia, dyspnoea, wheezing, chest discomfort/chest tightness, tachycardia, angioedema (swelling of face, lips, eyes, and tongue), flushing, rash, urticaria, pruritus, and gastrointestinal symptoms (vomiting, nausea, and diarrhoea)
- Four out of 16 (1%; 4/285) patients experienced a total of 5 episodes of acute systemic hypersensitivity reactions considered severe based on the presence of: cyanosis or oxygen saturation (SpO2) less than or equal to 92%, hypotension (systolic blood pressure below 90 mmHg in adults) or syncope
- Acute systemic hypersensitivity reactions were most frequent during induction and titration phase (5% of patients; 19 episodes over mean treatment duration of 12 months) and decreased in maintenance phase (2% of patients; 6 episodes over mean treatment duration of 28 months). The risk of an acute systemic hypersensitivity reaction occurring is 7 fold higher in induction/titration phase compared to maintenance phase
- Acute systemic hypersensitivity reactions generally occurred within the first hour after injection (88%; 22/25 episodes); however, reactions have occurred up to 24 hours after dosing
- Ten out of the 16 patients who experienced an acute systemic hypersensitivity reaction were re challenged and 4 patients had at least one recurrence. Seven out of the 16 patients discontinued treatment. All episodes resolved without sequelae

Prevention of acute systemic hypersensitivity

1. Premedication

- Premedication prior to each dose is required during induction and titration
- Patients should be pre-medicated with an H_1 antagonist, H_2 antagonist, and an antipyretic
- During maintenance, premedication should be reconsidered for subsequent injections based upon patient tolerability to PALYNZIQ®

2. Adrenaline

- Adrenaline injection device (auto injector or pre filled syringe/pen) should be prescribed to patients receiving this medicinal product. Patients should be instructed to carry adrenaline injection device with them at all times during PALYNZIQ® treatment
- Patients and the trained observer should be instructed to recognise the signs and symptoms of acute systemic hypersensitivity reactions, in the proper use of emergency injection of adrenaline, and requirement to seek immediate medical care upon its use
- The risks associated with adrenaline use should be considered when prescribing PALYNZIQ®. Refer to the adrenaline product information for complete information

3. Observer

- For at least the first 6 months of treatment, when the patient is self-injecting (i.e. when administration is not under healthcare professional supervision), an observer must be present during and for at least 60 minutes after each administration
- After 6 months of PALYNZIQ® treatment, the need for an observer should be reconsidered
- An observer is someone who is able to recognise the signs and symptoms of an acute systemic hypersensitivity reaction, can call for emergency medical support and administer adrenaline, if warranted

4. Initial injection

Prior to first dose of PALYNZIQ®, the patient and observer should be trained on the following:

- How to recognise the signs and symptoms of an acute systemic hypersensitivity reaction and to seek immediate medical care
- How to properly administer adrenaline injection device (auto injector or pre-filled syringe/pen)

Initial administration(s) should be performed under supervision of a healthcare professional and patients should be closely observed for at least 60 minutes following injection.

5. Competency in Independent Self-injection

The Healthcare Professional must ensure the following criteria are fulfilled prior to independent self-injection by the patient:

- Appropriate instruction for self-administration must be provided
- The patient/caregiver should be provided with the Important Information for Patients and Trained Observers for the Safe Use of PALYNZIQ®, Patient Alert Card and Package Leaflet
- Patient must demonstrate competency at self-injection
- Patient/Trained Observer must be provided with education and be able to recognise the signs and symptoms of acute systemic hypersensitivity reaction
- Patient must be provided with a prescription of adrenaline auto-injector and Patient/Trained Observer must have received education on how to use the auto-injector and the need to call for emergency medical support and administer adrenaline
- An observer is required for patients for at least the first 6 months of treatment for at least 60 minutes after each administration. After the first 6 months, the need for an observer should be based upon clinical judgement. The trained observer must be present during and for at least 60 minutes after PALYNZIQ® administration. The Trained Observer must be trained to recognise signs and symptoms of an acute systemic hypersensitivity reaction, to seek immediate medical care if a reaction occurs, and how to properly administer adrenaline injection device (auto-injector or pre-filled syringe/pen)

Management of hypersensitivity reactions including acute systemic hypersensitivity reaction

Acute systemic hypersensitivity reactions require treatment with adrenaline. For severe systemic hypersensitivity reactions or recurrence of acute systemic hypersensitivity reactions, patients should seek immediate medical care and PALYNZIQ® should be permanently discontinued.

Management of other hypersensitivity reactions should be based on the severity of the reaction. In clinical trials, this has included:

- Dosage adjustments
- Drug interruption
- Additional antihistamines
- Antipyretic
- Corticosteroids

Retreatment following acute systemic hypersensitivity reaction

Patients who experience a severe episode of acute systemic hypersensitivity reaction or recurrence of mild to moderate episode of acute systemic hypersensitivity reaction should permanently discontinue PALYNZIQ® treatment.
The prescribing physician should consider the risks and benefits of readministering the medicinal product following resolution of the first mild to moderate acute systemic hypersensitivity reaction.

Upon re-administration, the first dose must be administered with premedication under the supervision of a healthcare professional with the ability to manage acute systemic hypersensitivity reactions.

The prescribing physician should continue or consider resuming use of premedication.

Importance of the registry

In order to continue to monitor the safety of PALYNZIQ®, BioMarin is undertaking a multi-centre observational study to evaluate the long-term safety of subcutaneous injections of PALYNZIQ® in normal clinical practice. Prescribers are encouraged to participate in the registry and enrol patients who commence PALYNZIQ® treatment.

For further information contact **medinfo@bmrn.com.**

BIOMARIN®

Palynziq®
(pegvaliase) Injection

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