Abbreviated Prescribing Information (PI) (INTL): PALYNZIQ® (pegvaliase)

Refer to Summary of Product Characteristics for full information.

Presentation: 2.5 mg solution for injection in pre-filled syringe containing Palynziq® 2.5 mg pegvaliase in 0.5 ml solution. Palynziq® 10 mg solution for injection in pre-filled syringe containing 10 mg pegvaliase in 0.5 ml solution. Palynziq® 20 mg solution for injection in pre-filled syringe containing 20 mg pegvaliase in 1 ml solution. **Therapeutic indications:** 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 greater than 600 micromol/l) despite prior management with available treatment options. **Posology:** Before initiating treatment, blood phenylalanine level must be obtained. Monitoring of blood phenylalanine level is recommended once a month. Dietary phenylalanine intake should remain consistent until a maintenance dose is established. *Induction:* The recommended starting dose of Palynziq® is 2.5 mg administered once per week for 4 weeks. *Titration:* The dose should be escalated gradually based on tolerability to the daily maintenance dose required to achieve blood phenylalanine level of 120 to 600 micromol/l according to the table below. *Maintenance:* The maintenance dose is individualised to achieve patient's blood phenylalanine control (i.e., a phenylalanine level between 120 to 600 micromol/l) taking into account patient tolerability to Palynziq® and dietary protein intake (see table below). During titration and maintenance of Palynziq® treatment, patients may develop blood phenylalanine levels below 30 micromol/l. To manage hypophenylalaninaemia, dietary protein intake should be increased to appropriate levels, and then, if needed, the dose of Palynziq® should be reduced.

Recommended dosing regimen

	Dose[1] administered subcutaneously	**Duration prior to next dose increase**
Induction	2.5 mg once weekly	4 weeks[2]
Titration	2.5 mg twice weekly	1 week[2]
	10 mg once weekly	1 week[2]
	10 mg twice weekly	1 week[2]
	10 mg four times a week	1 week[2]
	10 mg daily	1 week[2]
Maintenance[3]	20 mg daily	12 weeks to 24 weeks[2]
	40 mg daily (2 consecutive injections of 20 mg pre-filled syringe)[4]	16 weeks[2]
	60 mg daily (3 consecutive injections of 20 mg pre-filled syringe)[4]	Maximum recommended dose

1 If blood phenylalanine levels are below 30 micromol/l, dietary protein intake should be increased to appropriate levels, and then, if needed, the dose of Palynziq® should be reduced.

2 Additional time may be required prior to each dose escalation based on patient tolerability with Palynziq®.

3 The maintenance dose is individualised to achieve blood phenylalanine levels between 120 to 600 micromol/l.

4 If multiple injections are needed for a single dose, injections should be administered at the same time of day and injection sites should be at least 5 cm away from each other. Doses should not be divided over the course of the day.

Administration: Subcutaneous use. Each pre-filled syringe is for single use only. Prior to first dose of Palynziq®, the patient should be trained by a healthcare professional on the signs and symptoms of an acute systemic hypersensitivity reaction and to seek immediate medical care if a reaction occurs, and how to properly administer adrenaline injection device. Due to the potential for an acute systemic hypersensitivity reaction, premedication prior to each dose is required during induction and titration (time prior to reaching blood phenylalanine levels less than 600 micromol/l while on a stable dose). Patients should be instructed to pre medicate with an H1 receptor antagonist, H2 receptor antagonist, and antipyretic. During maintenance, premedication may be reconsidered for subsequent injections based on patient tolerability to Palynziq®. Readministration following mild to moderate acute systemic hypersensitivity reactions: 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. Readministration for the first dose must be done under supervision of a healthcare professional with the ability to manage acute systemic hypersensitivity reactions. **Contraindications:** Severe systemic hypersensitivity reaction or recurrence of a mild to moderate acute systemic hypersensitivity reaction to pegvaliase, any of the excipients or another PEGylated medicinal product. **Warnings and precautions:** *Hypersensitivity reactions*, cover a group of terms that comprises acute systemic hypersensitivity reactions, other systemic hypersensitivity reactions such as angioedema and serum sickness which may have an acute or chronic presentation, and local hypersensitivity reactions such as injection site reactions or other skin reactions. Hypersensitivity reactions including anaphylaxis 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. The risk of a hypersensitivity reactions is 2.6 fold higher in induction/titration phase compared to the maintenance phase. Management of hypersensitivity reactions should be based on the severity of the reaction; in clinical trials, this has included dose adjustment, treatment interruption or discontinuation, additional antihistamines, antipyretics, and/or corticosteroids, adrenaline and/or oxygen. *Acute systemic hypersensitivity reactions (Type III)*, The underlying mechanism for acute systemic hypersensitivity reactions observed in clinical trials was non IgE mediated Type III (immune complex mediated) hypersensitivity. Manifestations of acute systemic hypersensitivity reactions 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). Acute systemic hypersensitivity reactions were considered severe based on the presence of cyanosis or oxygen saturation (SpO2) less than or equal to 92%, hypotension (systolic blood pressure below 90 mm Hg in adults) or syncope. Four out of 16 (1%, 4/285) patients experienced a total of 5 episodes of acute systemic hypersensitivity reactions that were considered severe. The risk of an acute systemic hypersensitivity reaction occurring is 6 fold higher in induction/titration phase compared to maintenance phase. Acute systemic hypersensitivity reactions require treatment with adrenaline and immediate medical care. An 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 an adrenaline injection device with them at all times during Palynziq® treatment. Patients and the observer should be instructed to recognise the signs and symptoms of acute systemic hypersensitivity reactions, in the proper emergency use of the adrenaline injection device, and the requirement to seek immediate medical care. The risks associated with adrenaline use should be reconsidered when prescribing Palynziq®. Refer to the adrenaline product information for complete information. For recurrence of a mild to moderate acute systemic hypersensitivity reaction patients should seek immediate medical care and Palynziq® should be permanently discontinued. Due to the potential for acute systemic hypersensitivity reactions, premedication prior to each dose is required during induction and titration (see section 4.2, Method of administration). Patients should be instructed to pre medicate with an H1 receptor antagonist, H2 receptor antagonist, and antipyretic. During maintenance, premedication may be considered for subsequent injections based on patient tolerability to Palynziq®. 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. Other systemic hypersensitivity reactions. For other severe systemic hypersensitivity reactions (e.g., anaphylaxis, severe angioedema, severe serum sickness), patients should seek immediate medical care and Palynziq should be permanently discontinued. *Re-administering following an acute systemic hypersensitivity reaction:* 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. *Dose titration and time to achieve response:* Time to response (achieving blood phenylalanine levels ≤ 600 micromol/l) varies among patients. The time to reach a response ranged from 0.5 to 54 months. The majority of patients (67%) reached a response by 18 months of total treatment. An additional 8% of patients responded to Palynziq® after 18 months of treatment. If a patient does not reach a clinically relevant blood phenylalanine reduction after 18 months of treatment, continuation should be reconsidered. The physician may decide, with the patient, to continue Palynziq® treatment in those patients who show other beneficial effects (e.g. ability to increase protein intake from intact food or improvement of neurocognitive symptoms). *Hypophenylalaninaemia: in clinical trials, 46% of the patients developed hypophenylalaninaemia (blood phenylalanine levels below 30 micromol/l on two consecutive measurements). The risk of hypophenylalaninaemia occurring is 2.1 fold higher in the maintenance phase compared to the induction/titration phase (see section 4.8).* Monitoring of blood phenylalanine level is recommended once a month. If a patient has a confirmed phenylalanine level below 30 micromol/l, dietary protein intake should be increased to appropriate levels, and then, if needed, the dose of Palynziq® should be reduced. In patients experiencing hypophenylalaninaemia despite appropriate levels of protein intake, dose reductions are expected to be most effective in managing hypophenylalaninaemia. Patients who develop hypophenylalaninaemia should be monitored every 2 weeks until blood phenylalanine level is within a clinically acceptable range. The long term clinical consequences of chronic hypophenylalaninaemia are unknown. Blood phenylalanine levels should be monitored more frequently prior to and during pregnancy. **Interaction with other medicinal products:** PEGylated proteins have the potential to elicit an immune response. Because antibodies bind to the PEG portion of pegvaliase, there may be potential for binding with other PEGylated therapeutics and increased hypersensitivity to other PEGylated injectables. **Pregnancy and lactation:** Palynziq® is not recommended during pregnancy, unless the clinical condition of the woman requires treatment with pegvaliase and alternative strategies to control phenylalanine levels have been exhausted should only be administered to breast-feeding women if the potential benefit is considered to outweigh the potential risk to the infant. **Effects on ability to drive and use machines:** Palynziq® has a minor influence on the ability to drive and use machines. Hypersensitivity reactions that include symptoms such as dizziness or syncope may affect the ability to drive and use machines. **Overdose:** In clinical trials, doses of pegvaliase were explored up to 150 mg/ day and no specific signs or symptoms were identified following these higher doses. No differences in the safety profile were observed. **Summary of the safety profile:** In clinical trials, the majority of patients experienced injection site reactions (90%), arthralgia (86%), and hypersensitivity reactions (75%). The most clinically significant hypersensitivity reactions include acute systemic hypersensitivity reaction (6%), angioedema (7%), and serum sickness (2%) In clinical trials, adverse reaction rates were highest in induction and titration phases (time prior to reaching blood phenylalanine levels less than 600 micromol/l while on a stable dose) coinciding with the period when titres of IgM and anti-PEG antibodies were highest. Rates decreased over time as the immune response matured **Tabulated list of adverse reactions:** Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System organ class	**Adverse reaction(s)**	**Induction/ Titration**	**Maintenance**
Blood and lymphatic system disorders	Lymphadenopathy	Common (9.8%)	Very common (16%)
Immune system disorders	Hypersensitivity reaction	Very common (65%)	Very common (60%)
	Acute systemic hypersensitivity reaction	Common (4.6%)	Common (1.7%)
	Angioedema	Common (5.6%)	Common (2.89%)
	Serum sickness	Common (2.1%)	Uncommon (0.6%)
	Anaphylaxis	Unknown	Unknown
Nervous system disorders	Headache	Very common (42%)	Very common (47%)
Respiratory, thoracic and mediastinal disorders	Cough	Very common (19%)	Very common (24%)
	Dyspnoea	Common (4.2%)	Common (7.3%)
Gastrointestinal disorders	Abdominal pain	Very common (19%)	Very common (30%)
	Nausea	Very common (25%)	Very common (28%)
	Vomiting	Very common (19%)	Very common (27%)
	Diarrhoea	Very common (13%)	Very common (28%)
Skin and subcutaneous tissue disorders	Alopecia	Common (6.7%)	Very common (21%)
	Urticaria	Very common (25%)	Very common (24%)
	Rash	Very common (33%)	Very common (24%)
	Pruritus	Very common (25%)	Very common (23%)
	Erythema	Very common (11%)	Common (6.7%)
	Skin exfoliation	Uncommon (0.4%)	Common (1.7%)
	Maculopapular rash	Common (3.5%)	Common (1.79%)
Musculoskeletal and connective tissue disorders	Arthralgia	Very common (79%)	Very common (67%)
	Myalgia	Very common (11%)	Very common (12%)
	Joint swelling	Common (6.0%)	Common (3.94%)
	Musculoskeletal stiffness	Common (4.2%)	Common (5.6%)
	Joint stiffness	Common (6.3%)	Common (2.2%)
General disorders and administration site conditions	Injection site reaction	Very common (90%)	Very common (66%)
	Fatigue	Very common (16%)	Very common (24%)
Investigations	Hypophenylalaninae-mia	Very common (15%)	Very common (65%)
	Complement factor C3 decreased	Very common (66%)	Very common (73%)
	Complement factor C4 decreased	Very common (64%)	Very common (39%)
	High sensitivity CRP levels increased	Very common (17%)	Common (13%)

For a detailed description of the adverse events please consult the Summary of Product Characteristics. **Special precautions for storage:** Store in a refrigerator (2°C-8°C). Do not freeze. Palynziq® may be stored in its sealed tray outside the refrigerator (below 25°C) for a single period up to 30 days with protection from sources of heat. After removal from the refrigerator, the product must not be returned to the refrigerator. **Marketing authorisation holder:** BioMarin International Limited. Shanbally, Ringaskiddy, County Cork, Ireland Detailed information on this medicinal product is available on the website of the European Medicines Agency: http://www.ema. europa.eu/ **Legal Classification:** Prescription-only Medicine. **Marketing authorisation number(s**): EU/1/19/1362/001-EU/1/19/1362/002-EU/1/19/1362/003-EU/1/19/1362/004. Date of first authorisation: May 2019. Date of revision of the text: April 2024

Healthcare professionals should report adverse events in accordance with their local requirements.

Adverse events should also be reported to BioMarin on + 1 415 506 6179 or drugsafety@bmrn.com