▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

- Acute systemic hypersensitivity reaction has been reported after administration of PALYNZIQ and may occur at any stage during treatment
- The first dose should be administered in a medical facility capable of managing acute systemic hypersensitivity reactions, patients should be monitored for 60 minutes after the dose
- It is recommended that ongoing doses be supervised by a trained observer who has been educated about the recognition and treatment of acute systemic hypersensitivity reaction, including the use of an adrenaline auto-injector
- Patients should be prescribed an adrenaline auto-injector to carry with them in case of acute systemic hypersensitivity reactions
- See sections 4.2 and 4.3

AUSTRALIAN PRODUCT INFORMATION - PALYNZIQ (pegvaliase)

1. NAME OF THE MEDICINE

Pegvaliase.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2.5 mg pre-filled syringe contains 2.5 mg pegvaliase in 0.5 mL solution.

Each 10 mg pre-filled syringe contains 10 mg pegvaliase in 0.5 mL solution.

Each 20 mg pre-filled syringe contains 20 mg pegvaliase in 1 mL solution.

The strength indicates the quantity of the phenylalanine ammonia lyase (rAvPAL) moiety of pegvaliase without consideration of the PEGylation.

The active substance is a covalent conjugate of the protein phenylalanine ammonia lyase (rAvPAL)* with NHS-methoxypolyethylene glycol (NHS-PEG).

* *Anabaena variabilis* rAvPAL produced by recombinant DNA technology in *Escherichia coli.*

The potency of this medicinal product should not be compared to any other PEGylated or non-PEGylated proteins of the same therapeutic class.

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Solution for injection.

Colourless to pale yellow, clear to slightly opalescent solution with pH 6.6 – 7.4.

2.5 mg pre-filled syringe:

Osmolality: 260 – 290 mOsm/kg

10 mg and 20 mg pre-filled syringe:

Osmolality: 285 – 315 mOsm/kg, viscous solution

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment with PALYNZIQ should be directed by physicians experienced in the management of PKU and in the context of a multidisciplinary team, including dietician.

Before initiating treatment, blood phenylalanine level must be obtained. Monitoring of blood phenylalanine level is recommended at least once a month. More frequent monitoring is recommended (e.g. weekly) when there are dose adjustments.

Dietary phenylalanine intake should remain consistent until a maintenance dose is established. Dietary advice should be obtained if blood phenylalanine drops below 120 micromol/L.

Dosage

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 Table 1.

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 1).

Table 1: 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 (see section 4.4 Special warnings and precautions for use - Hypophenylalaninaemia). Weekly monitoring is required until phenylalanine levels are within a clinically acceptable range.

[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 (see Method of administration).

Method of administration

Subcutaneous use. Product is for single use in one patient only. Discard any residue.

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; see section 4.8 Adverse effects). 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.

Initial administration(s) should be performed under supervision of a healthcare professional and patients should be closely observed for at least 60 minutes following each of these initial injection(s) (see sections 4.4 Special warnings and precautions for use and 4.8 Adverse effects).

Prior to first dose of PALYNZIQ, the patient should be trained 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 (auto-injector or pre-filled syringe/pen).

Patients should be instructed to carry an adrenaline injection device with them at all times during PALYNZIQ treatment.

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. An observer is someone who:

- would be present with the patient during and after PALYNZIQ administration,

- 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.

After 6 months of PALYNZIQ treatment, the need for an observer may be reconsidered.

Prior to independent self-injection, a healthcare professional should:

- train the patient and assess patient competency on proper self-administration of this medicinal product.
- train the observer to recognise 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 (auto-injector or pre-filled syringe/pen).

Re-administration 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 (see sections 4.3 Contraindications and 4.4 Special warnings and precautions for use). Re-administration for the first dose must be done under supervision of a healthcare professional with the ability to manage acute systemic hypersensitivity reactions.

The recommended injection sites on the body are: the front middle of the thighs and the lower part of the abdomen except for 5 cm directly around 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.

PALYNZIQ should not be injected into moles, scars, birthmarks, bruises, rashes, or areas where the skin is hard, tender, red, damaged, burned, inflamed, or tattooed. The injection site should be checked for redness, swelling, or tenderness.

Patients or caregiver should be advised to rotate sites for subcutaneous injections. If more than one injection is needed for a single dose, each injection site should be at least 5 cm away from another injection site.

PALYNZIQ is a clear to slightly opalescent, colourless to pale yellow solution. The solution should not be used if discoloured or cloudy or if visible particles are present.

Dosage adjustment

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. In patients experiencing hypophenylalaninaemia despite appropriate levels of protein intake, dose reductions are expected to be most effective in managing hypophenylalaninaemia (see section 5.2, Exposure-effect). Patients should be monitored every week until blood phenylalanine levels are within a clinically acceptable range (see section 4.4 Special warnings and precautions for use - Hypophenylalaninaemia).

If hypophenylalaninaemia develops prior to reaching daily dosing, the dose may be reduced to the previous titration dose. If hypophenylalaninaemia develops once daily dosing is reached, the dose may be reduced by at least 10 mg decrements to achieve and maintain blood phenylalanine levels in the clinically acceptable range. In patients experiencing hypophenylalaninaemia on 10 mg/day, the dose may be reduced to 5 mg/day.

4.3 CONTRAINDICATIONS

Severe systemic hypersensitivity reaction or recurrence of a mild to moderate acute systemic hypersensitivity reaction to pegvaliase, any of the excipients listed in section 6.1, or another PEGylated medicinal product (see section 4.4 Special warmings and precautions for use).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity reactions

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 (see Effect of PALYNZIQ on 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, corticosteroids, adrenaline, and/or oxygen (see sections 4.2, method of administration and 4.8).

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 (see sections 4.3 Contraindications and 4.8 Adverse effects).

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 (SpO_2) 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 considered when prescribing PALYNZIQ. Refer to 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 (see section 4.3). **Due to the potential for acute systemic hypersensitivity reactions, premedication prior to each dose is required during induction and titration (see section 4.2 Dose and 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 (see section 4.2 Dose and method of 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 (see section 4.3 Contraindications).

Re-administering following an acute systemic hypersensitivity reaction

The prescribing physician should consider the risks and benefits of re-administering 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).

Effect of PALYNZIQ on other PEGylated injectable 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. In a single dose study of PALYNZIQ in adult patients with PKU, two patients receiving concomitant injections of medroxyprogesterone acetate suspension containing PEG experienced hypersensitivity reactions. One of the two patients experienced a hypersensitivity reaction on day 15 after a single PALYNZIQ dose within 15 minutes following medroxyprogesterone acetate, and subsequently experienced an acute systemic hypersensitivity reaction on day 89 within 30 minutes after the next dose of medroxyprogesterone acetate injectable suspension. The second patient experienced a hypersensitivity reaction on day 40 after a single PALYNZIQ dose within 10 minutes following medroxyprogesterone acetate injectable suspension. In PALYNZIQ clinical trials, the majority of patients developed anti-PEG IgM and IgG antibodies after treatment with PALYNZIQ (see section 4.8). The impact of anti-PEG antibodies on the clinical effects of other PEG-containing medicinal products is unknown.

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 at least once a month. In case of hypophenylalaninaemia, dietary protein intake should be increased to appropriate levels, and then, if needed, the dose of PALYNZIQ should be reduced (see section 4.2 Dose and method of administration). 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.

Based on animal studies, hypophenylalaninaemia in pregnant women with PKU treated with PALYNZIQ may be associated with adverse fetal outcomes (see sections 4.6 Fertility, pregnancy and lactation). Blood phenylalanine levels should be monitored more frequently prior to and during pregnancy.

Use in the elderly

No data available.

Paediatric use

No data available.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been performed.

Effects of PALYNZIQ on other PEGylated injectable 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. Refer to Section 4.4 Special warnings and precautions for use. Examples of PEGylated injectable products include medroxyprogesterone acetate (used for contraception) and some mRNA COVID-19 vaccines.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No human data are available. In a rat fertility and embryofetal development study, male fertility was unaffected at subcutaneous doses up to 20 mg/kg/day (17 times the MHRD). However, at doses up to 20 mg/kg/day, impaired female fertility was noted, as indicated by lower numbers of corpora lutea and implantations, and a reduced litter size. These effects were associated with toxicity (decreased body weight, ovarian weight, and food consumption). No effects on female fertility were seen at 8 mg/kg/day SC (7 times the MRHD).

Use in pregnancy

Category D

There are no or limited amount of data from the use of PALYNZIQ in pregnant women. Animal studies have shown maternal reproductive toxicity that may have been associated with decreased blood phenylalanine concentrations below normal levels.

In a rabbit embryofetal development study, embryofetal lethality, lower fetal weights and multiple fetal malformations and/or variations (throughout the skeletal system, and in kidneys, lungs, and eyes) were noted at maternotoxic doses ≥ 2 mg/kg/day SC (marginally above the MRHD). No fetal malformations were seen in rats; however, an increased incidence in skeletal variations was seen at maternotoxic doses ≥ 8 mg/kg/day SC (NOAEL 2 mg/kg/day, marginally above the MRHD).

Uncontrolled blood phenylalanine levels (hyperphenylalaninaemia) before and during pregnancy are associated with increased risk for miscarriage, major birth defects (including microcephaly and major cardiac malformations), intrauterine fetal growth retardation and future intellectual disability with low IQ. In case of hypophenylalaninaemia during pregnancy, there is a risk of intrauterine fetal growth retardation. Additional risk to the unborn child due to hypophenylalaninaemia is not established.

Maternal blood phenylalanine levels must be strictly controlled between 120 and 360 micromol/L both before and during pregnancy. 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.

Use in lactation

It is unknown whether pegvaliase is excreted in human milk. Available data in animals have shown excretion of pegvaliase in milk. In the pups of these animals, systemic exposure of pegvaliase was not detected. A risk to infants cannot be excluded. Due to lack of human data, PALYNZIQ should only be administered to breast-feeding women if the potential benefit is considered to outweigh the potential risk to the infant.

4.7 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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

In clinical trials, the majority of patients experienced injection site reactions (93%), arthralgia (85%), and hypersensitivity reactions (75%). The most clinically significant hypersensitivity reactions include acute systemic hypersensitivity reaction (6%), angioedema (7%), and serum sickness (2%) (see sections 4.3 Contraindications and 4.4 Special warnings and precautions for use).

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 (see Description of selected adverse reactions section).

Tabulated list of adverse reactions

Table 2 provides adverse reactions in patients treated with PALYNZIQ.

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.

Table 2: Adverse reactions in patients treated with PALYNZIQ

System organ class	Adverse reaction(s)	Induction/Titration[1]	Maintenance
Blood and lymphatic system disorders	Lymphadenopathy	Common (9.8%)	Very common (16%)
Immune system disorders	Hypersensitivity reaction[2]	Very common (65%)	Very common (60%)
	Acute systemic hypersensitivity reaction[3]	Common (4.6%)	Common (1.7%)
	Angioedema[3]	Common (5.6%)	Common (2.8%)
	Serum sickness[3]	Common (2.1%)	Uncommon (0.6%)

System organ class	Adverse reaction(s)	Induction/Titration[1]	Maintenance
	Anaphylaxis[4]	Unknown	Unknown
Nervous system disorders	Headache	Very common (42%)	Very common (47%)
	Dizziness	Very common (20%)	Very common (20%)
Respiratory, thoracic and mediastinal disorders	Cough[2]	Very common (19%)	Very common (24%)
Gastrointestinal disorders	Abdominal pain[2,5]	Very common (19%)	Very common (30%)
	Nausea	Very common (25%)	Very common (28%)
	Vomiting	Very common (19%)	Very common (27%)
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%)
	Maculo-papular rash	Common (3.5%)	Common (1.79%)
Musculoskeletal and connective tissue disorders	Arthralgia[3]	Very common (79%)	Very common (67%)
	Myalgia	Very common (11%)	Very common (12%)
	Joint swelling	Common (6.0%)	Common (3.9%)
	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[3]	Very common (93%)	Very common (66%)
Investigations	Hypophenylalaninaemia	Very common	Very common

System organ class	Adverse reaction(s)	Induction/Titration[1]	Maintenance
		(15%)	(65%)
	Complement factor C3 decreased[6]	Very common (66%)	Very common (73%)
	Complement factor C4 decreased[6]	Very common (64%)	Very common (39%)
	High sensitivity CRP levels increased[7]	Very common (17%)	Very common (13%)

[1] Induction and titration phase reflects the time prior to reaching blood phenylalanine levels less than 600 micromol/L while on a stable dose. Once blood phenylalanine levels less than 600 micromol/L on stable dose was reached, patients were considered to be in the maintenance phase thereafter.

[2] Hypersensitivity reactions cover a group of terms, including acute systemic hypersensitivity reactions, and can manifest as a range of symptoms including angioedema, dyspnoea, serum sickness, rash, and urticaria.

[3] Refer to Warnings and Precautions.

[4] The frequency of anaphylaxis in the post-marketing setting cannot be determined.

[5] Abdominal pain reflects the following terms: abdominal pain, abdominal pain upper and abdominal discomfort.

[6] Complement factor C3/C4 decrease is defined by changing from normal or high baseline complement value to low post-baseline complement value.

[7] Reflects high sensitivity CRP (hsCRP) levels above upper limit of normal (greater than 0.287 mg/dl) over a 6 month period.

Description of selected adverse reactions

Arthralgia and other joint related signs and symptoms

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 can occur at any time during treatment. The risk of arthralgia occurring is 3.1-fold higher in induction/titration phase compared to maintenance phase.

Severe arthralgia (severe pain limiting self-care activities of daily living) was experienced in 5% of patients. Arthralgia episodes were managed with concomitant medicinal products (e.g., nonsteroidal anti-inflammatory drugs, glucocorticoids, and/or antipyretic), dose reduction, treatment interruption, or treatment withdrawal, and 97% of arthralgia episodes resolved by the time of study completion.

Persistent arthralgia (lasting at least 6 months) occurred in 7% of patients. Dose was not changed for 96% of episodes and all persistent arthralgia episodes resolved without sequelae.

Injection site reactions

Injection site reactions were reported in 93% of patients. The most common injection site reactions (occurring in at least 10% of patients) were reaction, erythema, bruising, pruritus, pain, swelling, rash, induration, and urticaria. The risk of injection site reactions occurring is 5.2-fold higher in induction/titration phase compared to maintenance phase.

Injection site reactions occurred as early as the first dose and can occur at any time during treatment. The mean duration of injection site reaction was 9 days, and 99% of injection site reactions resolved by the time of study completion.

Three injection site reactions consistent with granulomatous skin lesions were reported (each reaction occurring in one patient): granulomatous dermatitis (occurred 15 months after PALYNZIQ treatment and lasted 16 days), xanthogranuloma (occurred 12 months after PALYNZIQ treatment and lasted 21 months), and necrobiosis lipoidica diabeticorum (occurred 9 months after PALYNZIQ treatment and lasted 9 months). Necrobiosis lipoidica diabeticorum was treated with steroid injections and complicated

by *Pseudomonas* infection. All of these injection site reactions resolved. One patient reported soft tissue infection associated with mesenteric panniculitis, which resulted in treatment discontinuation.

Cutaneous reactions (not limited to the injection site) lasting ≥ 14 days

In clinical trials, 47% of patients treated with PALYNZIQ experienced cutaneous reactions (not limited to the injection site) lasting at least 14 days. The risk of cutaneous reactions lasting at least 14 days occurring is 1.5-fold higher in induction/titration phase compared to maintenance phase.

The most common cutaneous reactions (at least 5% of patients) reported were pruritus, rash, erythema, and urticaria. Other reactions reported included skin exfoliation, generalised rash, erythematous rash, maculo-papular rash, and pruritic rash. The mean (SD) duration of these reactions was 63 (76) days, and 86% of these reactions resolved by the time of study completion.

Immunogenicity

All patients treated with PALYNZIQ developed a sustained total anti-pegvaliase antibody (TAb) response with nearly all patients becoming positive by Week 4. Mean TAb titres were sustained through long-term treatment (greater than 3 years after treatment initiation). Anti-phenylalanine ammonia lyase (PAL) IgM was detected in nearly all treated patients by 2 months by 2 months after treatment initiation, with incidence and mean titres gradually decreasing over time. Anti-PAL IgG was detected in nearly all patients by 4 months and mean titres were relatively stable through long-term treatment. Pegvaliase induced anti-PEG IgM and IgG responses were detected in nearly all patients, with mean titres peaking at 1 to 3 months after treatment initiation and returning to baseline levels in most patients by 6 to 9 months after treatment initiation. Neutralising antibodies (NAb) capable of inhibiting PAL enzyme activity were detected in a majority of patients by one year after treatment initiation and mean titres were relatively stable through long-term treatment.

All 16 patients who experienced acute systemic hypersensitivity reactions tested negative for pegvaliase-specific IgE at or near the time of the acute systemic hypersensitivity reactions episode. These reactions were consistent with a Type III immune-complex mediated hypersensitivity mechanism and were most frequent in the early phases of treatment (during the induction and titration periods) when the early immune response was dominated by PEG IgM, PEG IgG and PAL IgM responses and C3/C4 levels were at their lowest. Hypersensitivity reactions decreased over time in maintenance as the incidence of these antibodies decreased, and C3/C4 levels returned towards baseline. Presence of antibody titres was not predictive of hypersensitivity reactions.

In clinical trials, a direct correlation between pegvaliase plasma exposure and blood phenylalanine reduction was observed. Pegvaliase plasma exposure was primarily driven by immune response to pegvaliase. Patients with lower antibody titres for all antibody analytes including NAb had higher pegvaliase concentrations due to less immune-mediated pegvaliase clearance. As a consequence, these patients were more likely to develop hypophenylalaninaemia. Patients with higher antibody titres required higher doses to overcome clearance and achieve blood phenylalanine reduction. However, due to the substantial variability in antibody titres between patients, no specific antibody titre was predictive of pegvaliase dose required to reach substantial blood phenylalanine reduction, or the development of hypophenylalaninaemia. During early treatment (less than 6 months after PALYNZIQ administration) when immune-mediated clearance was high and doses were low, patients with higher antibody titres achieved less blood phenylalanine reduction. Following maturation of the early immune response (more than 6 months after PALYNZIQ administration) and dose adjustment for managing blood phenylalanine control in long-term treatment, mean blood phenylalanine levels continued to decrease in patients who continued treatment (see section 5.1 Pharmacodynamic properties – clinical trials). Antibody titres were stable with long-term treatment and dose increases were not associated with increased antibody titres. Thus, mean dose levels also stabilized with long-term treatment with sustained therapeutic effect.

Paediatric population

No data are available in paediatric patients less than 16 years of age.

Twelve patients (11 patients from Study 301) aged 16 up to 18 years received PALYNZIQ treatment. Adverse reactions were similar in type and frequency to that of adult patients.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 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. For management of adverse reactions, see sections 4.4 Special warnings and precautions for use and 4.8 Adverse effects.

For further information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Other alimentary tract and metabolism products, Enzymes, ATC code: A16AB19

Mechanism of action

Pegvaliase is a PEGylated recombinant phenylalanine ammonia lyase enzyme that converts phenylalanine to ammonia and cinnamic acid that are primarily eliminated by liver metabolism.

Clinical trials

The effects of PALYNZIQ in the treatment of PKU have been demonstrated in patients with phenylketonuria in Study 301, an open-label study to initiate PALYNZIQ treatment, and Study 302, a follow-on study for efficacy assessment.

Study design

Study 301 an open-label randomised (1:1), multi-centre study of patients with PKU to assess the safety and tolerability of self-administered PALYNZIQ in an induction/titration/maintenance dose regimen. The 261 enrolled patients were aged 16 to 55 years (mean: 29 years) and had a baseline mean blood phenylalanine of 1233 micromol/L. At treatment initiation, 253 (97%) patients had inadequate blood phenylalanine control (blood phenylalanine levels above 600 micromol/L) and 8 patients had blood phenylalanine levels less than or equal to 600 micromol/L. Patients previously treated with sapropterin were required to discontinue treatment at least 14 days prior to first dose of PALYNZIQ. At baseline, 149 (57%) patients were receiving part of their total protein intake from medical food and 41 out of 261 (16%) patients were on a phenylalanine-restricted diet (defined as receiving greater than 75% of total protein intake from medical food). Patients initiated PALYNZIQ treatment with an induction regimen (2.5 mg once a week for 4 weeks) and were titrated in a stepwise manner (increased dose and frequency) to reach their randomised target dose of 20 mg once daily or 40 mg once daily. The duration of titration varied among patients and was based on patient tolerability (up to 30 weeks). For this study, the maintenance period was defined as at least 3 weeks dosing at randomised 20 mg or 40 mg once daily.

Of the 261 enrolled patients, 195 (75%) patients reached their randomised maintenance dose (103 patients in the 20 mg once daily arm, 92 patients in the 40 mg once daily arm). Patients in the 20 mg

once daily randomised arm reached their maintenance dose at a median time of 10 weeks (range: 9 to 29 weeks) and patients in the 40 mg once daily arm reached their maintenance dose at a median time of 11 weeks (range: 10 to 33 weeks). Of the 261 patients who enrolled in Study 301, 152 patients continued to the eligibility period of Study 302, and 51 patients continued directly from Study 301 into the long-term extension period of Study 302.

Study 302 was a follow-on study (from Study 301) and included: an open label eligibility period; a double-blind, placebo-controlled randomised discontinuation trial period (RDT), and a long-term open-label extension period.

Eligibility period

A total of 164 previously-treated PALYNZIQ patients (152 patients from Study 301, and 12 patients from other PALYNZIQ trials) continued treatment for up to 13 weeks.

Of the 164 patients that entered the eligibility period of Study 302, 86 patients met the eligibility criterion (achieved at least 20% mean blood phenylalanine reduction from pre-treatment baseline at their randomised dose within 13 weeks) and continued to the RDT, 12 patients discontinued treatment, and 57 patients did not enter the RDT and continued PALYNZIQ treatment in the long-term extension period of Study 302, where they were allowed to increase dose.

Results

Overall treatment experience from Study 301 and Study 302

At the time of completion of the studies, 188 out of the 261 patients received treatment for at least 1 year, 4 patients completed treatment, and 69 discontinued treatment in the first year. Of these 188 patients, 165 patients received treatment for at least 2 years, 22 patients discontinued in the second year, and 9 patients discontinued after 2 years of treatment. Of the 100 patients who discontinued treatment, 40 patients discontinued due to an adverse event, 29 patients discontinued due to patient decision, 10 patients discontinued due to physician decision, and 21 patients discontinued to other reasons (e.g. lost to follow-up, pregnancy, or protocol deviation).

Efficacy results over time are presented in Table 4 and Figure 1.

Phenylalanine levels over time

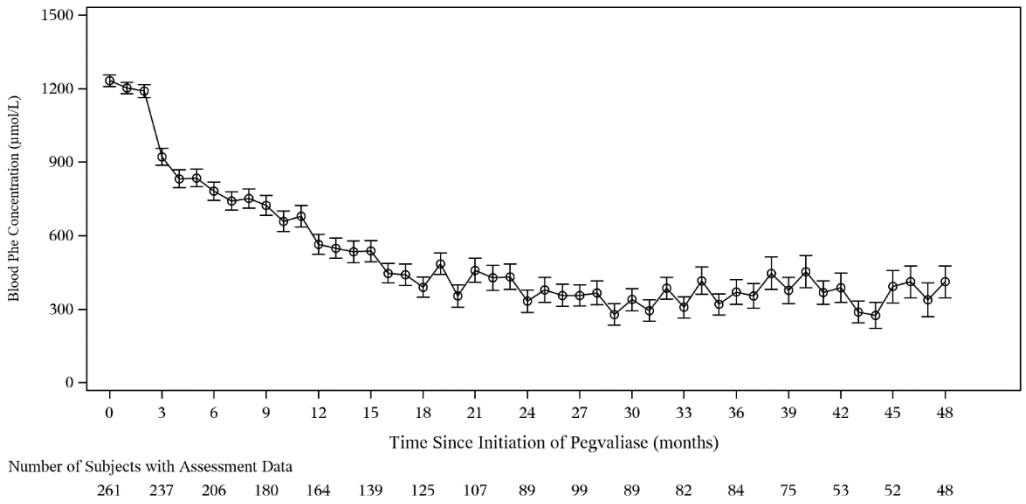
Mean blood phenylalanine levels reduced from 1233 micromol/L at baseline to 565 micromol/L at Month 12 (n=164) and 333 micromol/L at Month 24 (n=89), and these reductions in mean blood phenylalanine levels were maintained through Month 36 (371 micromol/L; n=84) (see Table 4 and Figure 1). Median change from baseline was -634 micromol/L at Month 12, -968 micromol/L at Month 24, and -895 micromol/L at Month 36.

Of 253 patients who had inadequate blood phenylalanine control (blood phenylalanine levels above 600 micromol/L) at baseline in Study 301:

- 54% of patients, 69% of patients, and 72% of patients reached blood phenylalanine level ≤ 600 micromol/L by 12 months, 24 months, and 36 months, respectively;

  44% of patients, 62% of patients, and 67% of patients reached blood phenylalanine level ≤ 360 micromol/L by 12 months, 24 months, and 36 months, respectively.

Figure 1: Mean (SE) phenylalanine levels over time



Randomised discontinuation trial (RDT) period

In the double-blind, placebo-controlled RDT, patients were randomised in a 2:1 ratio to either continue their randomised dosing (20 mg/day or 40 mg/day) or receive matching placebo for 8 weeks.

The primary endpoint was change from RDT baseline to RDT Week 8 in blood phenylalanine levels. PALYNZIQ-treated patients were able to maintain their blood phenylalanine reductions compared to the placebo patients whose blood phenylalanine levels returned to their pre-treatment baseline levels after 8 weeks ($p < 0.0001$, see Table 3).

Table 3: LS Mean change from RDT baseline in blood phenylalanine concentration (micromol/L) at RDT Week 8 in patients with PKU (Study 302)

Randomised study arm	Blood phenylalanine concentration (micromol/L) Mean (SD)			LS mean change from Study 302 RDT baseline to Week 8 (95% CI)	Treatment difference in LS mean change (95% CI) P-value[2]
	Pre-treatment baseline[1]	Study 302 RDT baseline	Study 302 RDT Week 8		
PALYNZIQ 20 mg once daily[3]	1450.2 (310.5) n = 29	596.8 (582.8) n = 29	553.0 (582.4) n = 26	-23.3 (-156.2, 109.7)	-973.0 (-1204.2, -741.9) p < 0.0001
Placebo 20 mg once daily[4]	1459.1 (354.7) n = 14	563.9 (504.6) n = 14	1509.0 (372.6) n = 13	949.8 (760.4, 1139.1)	
PALYNZIQ 40 mg once daily[3]	1185.8 (344.0) n = 29	410.9 (440.0) n = 29	566.3 (567.5) n = 23	76.3 (-60.2, 212.8)	-588.5 (-830.1, -346.9) p < 0.0001
Placebo 40 mg once daily[4]	1108.9 (266.8) n = 14	508.2 (363.7) n = 14	1164.4 (343.3) n = 10	664.8 (465.5, 864.1)	

[1] Blood phenylalanine level prior to initiating treatment with PALYNZIQ.

[2] Based on the mixed model repeated measures (MMRM) method, with treatment arm, visit, and treatment arm-by-visit interaction (the time profile of blood phenylalanine changes is assessed separately for each treatment arm) as factors adjusting for baseline blood phenylalanine concentration.

[3] Nine patients were excluded from the Week 8 analysis from the PALYNZIQ treatment arms (20 mg/day or 40 mg/day): 4 patients did not complete the RDT due to adverse events (1 patient discontinued treatment and 3 patients transitioned to the long-term extension period) and the remaining 5 patients who did not complete phenylalanine assessment within the window for Week 8 (Day 43 to 56).

[4] Five patients were excluded from the Week 8 analysis from the placebo arms (20 mg/day or 40 mg/day): 1 patient did not complete the RDT due to adverse event transitioned to the long-term extension period and the remaining 4 patients who did not complete phenylalanine assessment within the window for Week 8 (Day 43 to 56).

Symptoms of inattention and mood were also evaluated during this period. No differences were observed in inattention and mood between patients randomised to placebo versus those randomised to PALYNZIQ during this 8-week duration.

Long-term extension period

Patients continued PALYNZIQ treatment in the long-term open-label extension period and dose was adjusted (5, 10, 20, 40 and 60 mg/day) by the physician to achieve further blood phenylalanine reductions and maintain previously achieved phenylalanine levels.

ADHD inattention and PKU-POMS confusion over time

Symptoms of inattention were assessed using the inattention subscale of the investigator-rated Attention Deficient Hyperactivity Disorder Rating Scale (ADHD-RS IV). The ADHD-RS IV inattention subscale ranges from 0 to 27, higher scores indicate a greater degree of impairment, and a score below 9 indicates that the patient is asymptomatic (i.e. has a score that is in the normative range). Results for ADHD inattention subscale over time are shown in Table 4. Mean reduction (suggesting improvement) from baseline ADHD-RS inattention was above the minimally clinically important difference (MCID) for adults with ADHD (defined as a reduction of at least 5.2) at Month 18 (n=168; a reduction of 5.3), Month 24 (n=159; a reduction of 5.9) and Month 36 (n=142; a reduction of 6.6). In patients with baseline ADHD inattention scores > 9 (suggesting symptoms of inattention at baseline), mean reduction in ADHD inattention score from baseline (suggesting improvement) was above the MCID estimated for adults with ADHD at Month 12 (n=80; a reduction of 7.8), Month 18 (n=78; a reduction of 8.9), Month 24 (n=76; a reduction of 9.6) and Month 36 (n=66; a reduction of 10.7).

Symptoms of mood (confusion, fatigue, depression, tension-anxiety, vigour, and anger domains) were evaluated using the Profile of Mood States (POMS) tool that has been modified to be specific to PKU (PKU-POMS). The PKU-POMS confusion subscale (ranging from 0 to 12 points with higher scores indicating greater degree of impairment) was considered most sensitive to changes in blood phenylalanine levels. Results for PKU-POMS confusion subscale over time are shown in Table 4. Mean change from baseline PKU-POMS confusion subscale (suggesting improvement) was above MCID (defined as a reduction of at least 1) at Month 12 (n=130; a reduction of 1.6), Month 18 (n=123; a reduction of 2), Month 24 (n=116; a reduction of 2.2) and Month 36 (n=103; a reduction of 2.2).

Changes in protein intake from intact food over time

Median protein intake from intact food increased at Month 12 (4 g increase from baseline), Month 24 (14 g increase from baseline) and Month 36 (20 g increase from baseline).

Table 4: Efficacy results at Month 12, Month 18, Month 24 and Month 36 in PALYNZIQ-treated patients

	Baseline	Month 12	Month 18	Month 24	Month 36
Blood phenylalanine[1]					

	Baseline	Month 12	Month 18	Month 24	Month 36
N	261	164[2]	125[2]	89[2]	84[2]
Mean (SD) blood phenylalanine (micromol/L)	1233 (386)	565 (531)	390 (469)	333 (441)	371 (459)
Change from baseline (micromol/L) Mean (SD) Median	-	 -662 (588) -634	 -883 (565) -920	 -882 (563) -968	 -911 (563) -895
ADHD inattention[3] subscale (investigator-rated)					
N	253	178	175	166	147
Mean (SD) inattention score	9.8 (6.1)	5 (4.9)	4.6 (4.7)	4.3 (4.6)	3.4 (4.5)
Change from baseline inattention score (n)[4] Mean (SD) Median	-	 n=172 -4.7 (5.6) -4	 n=168 -5.3 (5.9) -5	 n=159 -5.9 (6.1) -5	 n=142 -6.6 (6.1) -5
ADHD inattention[3] subscale (investigator-rated) with baseline score > 9					
N	116	80	78	76	66
Mean (SD) inattention score	15.3 (4.1)	7.6 (4.9)	6.6 (5)	5.9 (4.9)	4.9 (5.3)
Change from baseline inattention score (n)[4] Mean (SD) Median	-	 n=80 -7.8 (5.5) -7	 n=78 -8.9 (5.8) -9	 n=76 -9.6 (5.9) -10	 n=66 -10.7 (6.0) -12
PKU-POMS confusion[3] subscale (self-rated)					
N	170	181	178	168	152
Mean (SD) confusion score	4 (2.7)	2.4 (2.1)	2.1 (2.2)	2 (2.1)	1.9 (2.1)
Change from baseline confusion score (n)[4] Mean (SD) Median	-	 n=130 -1.6 (2.5) -1	 n=123 -2 (2.8) -2	 n=116 -2.2 (2.7) -2	 n=103 -2.2 (3.0) -2
Protein intake from intact food (g)					
N	250	160	111	83	80
Mean (SD)	39 (28)	47 (29)	50 (27)	55 (27)	66 (27)
Change from baseline protein intake (n)[4] Mean (SD) Median	-	 n=154 9 (25) 4	 n=106 12 (25) 9	 n=80 16 (27) 14	 n=78 24 (31) 20

[1] Post-baseline phenylalanine values were mapped to the closest monthly visit (i.e. within a 1-month window).

[2] Reflects number of patients who reached time point (Month 12/Month 18/Month 24/Month 36) of treatment at the time of the data cut-off and had a scheduled phenylalanine assessment for that time point.

[3] Post-baseline ADHD-inattention/PKU-POMS confusion values were mapped to the closest 3-month visit (i.e. within a 3-month window).

[4] Change from baseline was based on subjects with available measurements at both time points. Not all subjects had a baseline ADHD inattention score and POMS confusion score taken at the start of the study.

Impact of blood phenylalanine reduction on ADHD inattention and PKU-POMS confusion

An analysis of ADHD inattention and PKU-POMS confusion subscales by change in blood phenylalanine from baseline quartiles showed that patients with the largest phenylalanine reductions experienced the greatest improvements in ADHD inattention and PKU-POMS confusion subscales.

Paediatric population

No data are available in paediatric patients less than 16 years of age.

Of the 261 patients in Study 301, 11 patients were aged between 16 and 18 years at enrolment. All 11 patients had inadequate blood phenylalanine control (blood phenylalanine levels above 600 micromol/L) at baseline. These patients received the same induction/titration/maintenance regimen as patients aged 18 years and older in this study. Mean (SD) change from baseline was 20 (323) micromol/L at Month 12 (n=9), -460 (685) micromol/L at Month 24 (n=5), and -783 (406) micromol/L at Month 36 (n=5). Of the 11 patients initially enrolled in Study 301, 3 patients reached blood phenylalanine levels ≤ 600 micromol/L by 12 months, 7 patients reached this threshold by 24 months, and 8 patients reached this threshold by 36 months.

5.2 PHARMACOKINETIC PROPERTIES

Pegvaliase is a PEGylated recombinant phenylalanine ammonia lyase (rAvPAL), derived from the cyanobacterium *Anabaena variabilis* expressed in *Escherichia coli*. The purpose of the PEGylation of rAvPAL is to reduce immune recognition of the rAvPAL bacterial protein and increase the half-life.

The pharmacokinetics of pegvaliase exhibit high inter-patient and intra-patient variability due to the heterogeneity of the immune response in adult patients with PKU. Immune response affects clearance and time to reach steady state. The immune response stabilises over 6 to 9 months of total treatment.

Absorption

Following a single subcutaneous dose (0.01, 0.03 or 0.1 mg/kg), pegvaliase is absorbed slowly with a median t_{max} of 3.5 to 4 days (individual range of 2.5 to 7 days). The bioavailability is not affected by the different injection sites on the body (see section 4.2 Dose and method of administration). The absolute bioavailability in humans is unknown.

Distribution

Mean (SD) for apparent volume of distribution (Vz/F) at steady state following 20 mg and 40 mg doses was 26.4 L (64.8 L) and 22.2 L (19.7 L) respectively.

Metabolism

Following cellular uptake, the metabolism of phenylalanine ammonia lyase (PAL) is expected to occur via catabolic pathways and be degraded into small peptides and amino acids; the PEG molecule is metabolically stable and expected to be separated from PAL protein and primarily eliminated by renal filtration.

Excretion

Pegvaliase is primarily cleared by immune-mediated mechanisms following repeat dosing. In clinical studies, anti-PAL, anti-PEG and anti-pegvaliase have been identified as IgG and IgM mainly. Relatively low titres of IgE has also been observed. In maintenance phase of the treatment, steady state is expected 4 to 24 weeks after maintenance dose started. A mean (SD) half-life at 20 mg and 40 mg were 47.3 hours (41.6 hours) and 60.2 hours (44.6 hours), respectively. Individual values for half-life range from 14 to 132 hours. The PEG molecule is expected to be primarily eliminated by renal filtration.

Linearity/nonlinearity

During dose escalation from 20 mg/day to 40 mg/day and 40 mg/day to 60 mg/day, a greater dose proportional increase in exposure was observed.

Specific populations

Analysis of pegvaliase concentration data from clinical trials indicated that body weight, gender and age did not have a notable effect on pegvaliase pharmacokinetics. No clinical studies have been conducted to evaluate the effect of renal or hepatic impairment on the pharmacokinetics of pegvaliase.

Exposure effect

A PK/PD analysis using the Phase III data demonstrated an inverse pegvaliase exposure-phenylalanine response relationship, which could be influenced by dietary phenylalanine intake. At lower plasma pegvaliase Ctrough concentrations < 10,000 ng/ml, patients with higher dietary phenylalanine intake tend to have higher blood phenylalanine levels compared to patients with the same Ctrough concentration and lower dietary phenylalanine intake, suggesting saturation of the enzyme (i.e. rAvPAL). At high pegvaliase Ctrough concentrations ≥ 10,000 ng/ml, the majority of the blood phenylalanine levels (97%) are ≤ 30 micromol/l, even when dietary phenylalanine intake is high. Therefore, a reduction in pegvaliase dose should be considered in patients experiencing hypophenylalaninaemia despite appropriate levels of protein intake (see section 4.2 Dose and method of administration).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No genotoxicity studies have been performed with pegvaliase.

Carcinogenicity

No long-term studies in animals to evaluate carcinogenic potential have been performed with pegvaliase.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Trometamol

Trometamol hydrochloride

Sodium chloride

Cinnamic acid

Water for injections

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 SHELF LIFE

2 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C (Refrigerate. 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.

6.5 NATURE AND CONTENTS OF CONTAINER

1 ml pre-filled syringe made of Type I borosilicate glass, equipped with a stainless steel 26 gauge needle, needle safety device, polypropylene plunger rod, and chlorobutyl rubber syringe stopper with fluoropolymer coating. The automatic needle guard is composed of a polycarbonate transparent needle guard and a stainless steel spring inside the needle guard.

Pre-filled syringe 2.5 mg (white plunger):

Each carton contains 1 pre-filled syringe.

Pre-filled syringe 10 mg (green plunger):

Each carton contains 1 pre-filled syringe.

Pre-filled syringe 20 mg (blue plunger):

Each carton contains 1 or 10 pre-filled syringes.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. After injection, the needle automatically retracts into the needle guard safely covering the needle.

Instructions for the preparation and administration of PALYNZIQ are given in the package leaflet.

6.7 PHYSICOCHEMICAL PROPERTIES

Pegvaliase is rAvPAL conjugated with linear 20 kDa NHS-PEG at a degree of substitution of 28 to 44 moles of polymer/mole of protein. The average molecular mass is approximately 1,000 kDa of which the protein moiety constitutes approximately 248 kDa.

Chemical structure:

rAvPAL Primary Amino Acid Sequence

1 MKTLSQAQSK TSSQQFSFTG NSSANVIIGN QKLTINDVAR VARNGTLVSL
51 TNNTDILQGI QASCDYINNA VESGEPIYGV TSGFGGMANV AISREQASEL
101 QTNLVWFLKT GAGNKLPLAD VRAAMLLRAN SHMRGASGIR LELIKRMEIF
151 LNAGVTPYVY EFGSIGASGD LVPLSYITGS LIGLDPSFKV DFNGKEMDAP
201 TALRQLNLSP LTLLPKEGLA MMNGTSVMTG IAANCVYDTQ ILTAIAMGVH
251 ALDIQALNGT NQSFHPFIHN SKPHPGQLWA ADQMISLLAN SQLVRDELDG
301 KHDYRDHELI QDRYSLRCLP QYLGPIVDGI SQIAKQIEIE INSVTDNPLI
351 DVDNQASYHG GNFLGQYVGM GMDHLRYYIG LLAKHLDVQI ALLASPEFSN
401 GLPPSLLGNR ERKVNMGLKG LQICGNSIMP LLTFYGNSIA DRFPTHAEQF
451 NQNINSQGYT SATLARRSVD IFQNYVAIAL MFGVQAVDLR TYKKTGHYDA
501 RASLSPATER LYSAVRHVVG QKPTSDRPYI WNDNEQGLDE HIARISADIA
551 AGGVIVQAVQ DILPSLH

CAS number:

1585984-95-7

7. MEDICINE SCHEDULE (POISON STANDARD)

S4 – Prescription Only Medicine

8. SPONSOR

BioMarin Pharmaceutical Australia Pty Ltd
119 Willoughby Road
Crows Nest, NSW 2065

For enquiries about PALYNZIQ, contact *medinfoasia@bmrn.com* or call BioMarin Australia on 1800 387 876.

To report adverse events, contact *drugsafety@bmrn.com* or call BioMarin Australia on 1800 387 876.

9. DATE OF FIRST APPROVAL

14 July 2021

10. DATE OF REVISION

09 August 2022

Summary table of changes

Section changed	Summary of new information
4.8	Addition of dizziness as an adverse reaction, addition of dyspnoea as a symptom of hypersensitivity reaction