ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼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. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Palynziq 2.5 mg solution for injection in pre-filled syringe
Palynziq 10 mg solution for injection in pre-filled syringe
Palynziq 20 mg solution for injection in pre-filled syringe

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 protein of the same therapeutic class. For more information, see section 5.1.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (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 (blood phenylalanine levels greater than 600 micromol/l) despite prior management with available treatment options.

4.2 Posology and method of administration

Treatment with Palynziq should be directed by physicians experienced in the management of PKU.

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.

Dosing regimens

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, Hypophenylalaninaemia).
[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).

Dose adjustments
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 2 weeks until blood phenylalanine levels are within a clinically acceptable range (see section 4.4, 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.

Special populations

Paediatric population
The safety and efficacy of Palynziq in paediatric patients from birth to less than 16 years have not been established. No data are available.

Currently available data on patients aged 16 up to 18 years are described in section 4.8 and 5.1. Posology is the same in these patients as in adults.

Method of administration

Subcutaneous use. Each pre-filled syringe is for single use only.

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). 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 and 4.8).

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 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).

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 (see sections 4.3 and 4.4). Readministration 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.

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).

4.4 Special warnings and precautions for use

Hypersensitivity reactions

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 (see Effect of Palynziq on other PEGylated injectable medicinal products).

In clinical trials, 16 out of 285 (6%) patients experienced 25 acute systemic hypersensitivity reactions of any severity. Acute systemic hypersensitivity reactions were managed by administration of adrenaline (44%; 11/25 episodes), corticosteroids (56%; 14/25 episodes), antihistamines (56%; 14/25 episodes), and/or oxygen (8%; 2/25 episodes). Four out of 16 (1%; 4/285) patients experienced a total of 5 episodes of acute systemic hypersensitivity reactions that were considered severe (see sections 4.3 and 4.8). The underlying mechanism for acute systemic hypersensitivity reactions observed in clinical trials was non-IgE mediated Type III (immune-complex mediated) hypersensitivity (see section 4.8).

In clinical trials, serum sickness was reported in 7 out of 285 (2%) patients. Three out of 7 (1%) patients had severe serum sickness (see section 4.8).

Management of hypersensitivity reactions should be based on the severity of the reaction; in clinical trials, this has included dose adjustment, treatment interruption, additional antihistamines, antipyretics, and/or corticosteroids.

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 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 the adrenaline product information for complete information.

Due to the potential for an acute systemic hypersensitivity reaction, 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 (see section 4.2, Method of administration).

For severe systemic hypersensitivity reactions or 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). 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 readministration, the first dose must be administered with premedication under the supervision of a healthcare professional with the ability to manage acute systemic hypersensitivity reactions. 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 30 months. The majority of patients (66%) reached a response by 18 months of total treatment. An additional 7% 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, 125 out of 285 (44%) patients developed a total of 237 episodes of hypophenylalaninaemia (blood phenylalanine levels below 30 micromol/l on two consecutive measurements). Hypophenylalaninaemia occurred during titration and maintenance phase, as early as 51 days and up 1405 days into Palynziq treatment (median: 393 days from Palynziq treatment initiation). The median duration was 161 days (range: 35, 1408). Patients who developed hypophenylalaninaemia during the studies were advised to increase their protein intake from intact foods and/or reduce Palynziq dose.

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 (see section 4.2). 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 foetal outcomes (see sections 4.6 and 5.3). Blood phenylalanine levels should be monitored more frequently prior to and during pregnancy.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per pre-filled syringe, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of Palynziq in pregnant women. Animal studies have shown maternal reproductive toxicity that was associated with decreased blood phenylalanine concentrations below normal levels (see section 5.3).

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 foetal growth retardation and future intellectual disability with low IQ. In case of hypophenylalaninaemia during pregnancy, there is a risk of intrauterine foetal 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.

Breast-feeding

It is unknown whether pegvaliase is excreted in human milk. Available toxicological 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.

Fertility

No human data are available. Reduced implantations were observed in normal female rats after administration of Palynziq (see section 5.3).

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 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 and 4.4).

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 (12%)
Immune system disorders	Hypersensitivity reaction[2]	Very common (65%)	Very common (58%)
	Acute systemic hypersensitivity reaction[3]	Common (4.6%)	Common (1.7%)
	Angioedema[3]	Common (5.6%)	Common (2.9%)
	Serum sickness[3]	Common (2.1%)	Uncommon (0.6%)
Nervous system disorders	Headache	Very common (42%)	Very common (46%)
Respiratory, thoracic and mediastinal disorders	Cough[2]	Very common (19%)	Very common (21%)
Gastrointestinal disorders	Abdominal pain[2,4]	Very common (19%)	Very common (27%)
	Nausea	Very common (25%)	Very common (27%)
	Vomiting	Very common (19%)	Very common (25%)
Skin and subcutaneous tissue disorders	Alopecia	Common (6.7%)	Very common (22%)
	Urticaria	Very common (25%)	Very common (21%)
	Rash	Very common (33%)	Very common (23%)
	Pruritus	Very common (25%)	Very common (22%)
	Erythema	Very common (11%)	Common (5.7%)
	Skin exfoliation	Uncommon (0.4%)	Common (1.7%)
	Maculo-papular rash	Common (3.5%)	Common (2.9%)
Musculoskeletal and connective tissue disorders	Arthralgia[3]	Very common (78%)	Very common (62%)
	Myalgia	Very common (11%)	Very common (11%)
	Joint swelling	Common (6.0%)	Common (3.4%)
	Musculoskeletal stiffness	Common (4.2%)	Common (5.1%)
	Joint stiffness	Common (6.3%)	Common (2.3%)
General disorders and administration site conditions	Injection site reaction[3]	Very common (90%)	Very common (64%)
Investigations	Hypophenylalaninaemia	Very common (15%)	Very common (61%)
	Complement factor C3 decreased[5]	Very common (66%)	Very common (73%)

System organ class	Adverse reaction(s)	Induction/Titration[1]	Maintenance
	Complement factor C4 decreased[5]	Very common (64%)	Very common (35%)
	High sensitivity CRP levels increased[6]	Very common (17%)	Common (9.1%)

[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, serum sickness, rash, and urticaria.
[3] Refer to Description of selected adverse reactions section.
[4] Abdominal pain reflects the following terms: abdominal pain, abdominal pain upper and abdominal discomfort.
[5] Complement factor C3/C4 decrease is defined changing from normal or high baseline complement value to low post-baseline complement value.
[6] 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

Hypersensitivity reactions
In clinical trials, 213 out of 285 (75%) patients experienced hypersensitivity reactions. The most common hypersensitivity reactions (occurring in at least 10% of patients) were rash, urticaria, and hypersensitivity. Hypersensitivity reactions were most frequent during induction and titration phase (65% of patients; 921 episodes over mean treatment duration of 12 months) and decreased in maintenance phase (58% of patients; 491 episodes over mean treatment duration of 28 months). The risk of a hypersensitivity reaction occurring is 2.6-fold higher in induction/titration phase compared to maintenance phase.

Hypersensitivity reactions occurred as early as the first dose and can occur at any time during treatment. Hypersensitivity reactions were managed with dose reduction (3% of episodes), treatment interruption (5% of episodes), treatment withdrawal (2% of episodes), and/or concomitant medicinal products. The mean duration of hypersensitivity reactions was 7 days, and ranged less than 1 day to 227 days; 89% of hypersensitivity reactions had a duration of less than 14 days, 0.4% of hypersensitivity reactions persisted at least 180 days, and 99% of hypersensitivity reactions resolved by the time of the data cut-off.

Acute systemic hypersensitivity reactions
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 (SpO_2) less than or equal to 92%, hypotension (systolic blood pressure below 90 mm Hg 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. Reactions were managed by administration of adrenaline (10/16 patients; 11/25 episodes), corticosteroids, antihistamines, and/or oxygen under emergency medical care. Ten out of the 16 patients who experienced an acute systemic hypersensitivity reaction were rechallenged and 4 patients had at least one recurrence. Seven out of the 16 patients discontinued treatment. All episodes resolved without sequelae (see Immunogenicity section).

Angioedema
In clinical trials, 21 out of 285 (7%) patients experienced 37 episodes of mild to moderate episodes of angioedema (symptoms include one or more of the following: pharyngeal oedema, swollen tongue, lip swelling, mouth swelling, eyelid oedema and face oedema) occurring independent of acute systemic hypersensitivity reactions. Angioedema was most frequent during induction and titration phase (6% of patients; 27 episodes over mean treatment duration of 12 months) and decreased in maintenance phase (3% of patients; 10 episodes over mean treatment duration of 28 months). The risk of angioedema occurring is 4.5-fold higher in induction/titration phase compared to maintenance phase.

Angioedema occurred as early as 4 days and up to 1222 days into Palynziq treatment (median: 91 days from Palynziq treatment initiation). Of the 9 angioedema episodes where time to onset was evaluable, 5 episodes occurred within 24 hours of injection, 4 episodes occurred between 24 hours and up to 29 days of injection. Eighteen out of 21 patients who experience angioedema were re-challenged and 5 patients had at least one recurrence. Angioedema was managed with dose reduction (3 episodes; 8%), treatment interruption (5 episodes; 14%), treatment withdrawal (3 episodes; 8%), and/or concomitant medicinal products. All episodes resolved without sequelae.

Angioedema can also present as one of the symptoms of an acute systemic hypersensitivity reaction.

Serum sickness
In clinical trials, serum sickness was reported in 7 out of 285 (2%) patients. Serum sickness was most frequent during induction and titration phase (2% of patients; 6 episodes over mean treatment duration of 12 months) and decreased in maintenance phase (0.6% of patients; 1 episode over mean treatment duration of 28 months). The risk of serum sickness occurring is greater than 2-fold higher in induction/titration phase compared to maintenance phase.

Serum sickness occurred as early as 10 days and up to 232 days into Palynziq treatment (median: 13 days from Palynziq treatment initiation). Of the 5 serum sickness episodes where time to onset was evaluable, 1 episode occurred within 1 hour of injection and 4 episodes occurred between 24 hours and up to 5 days following injection. The mean duration of serum sickness was 5 days and ranged from 1 to 8 days.

Three of these patients experienced severe serum sickness (3/285; 1%), which resulted in treatment discontinuation (2 patients) or treatment interruption (1 patient). Five out of the 7 patients who experienced serum sickness continued treatment without a recurrence, and managed serum sickness with treatment interruption, dose reduction and/or concomitant medicinal products. All serum sickness reactions resolved without sequelae.

Arthralgia and other joint related signs and symptoms
In clinical trials, 241 out of 285 (85%) 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. Arthralgia was most frequent during induction and titration phase (78% of patients; 1264 episodes over mean treatment duration of 12 months) and decreased in maintenance phase (62% of patients; 612 episodes over mean treatment duration of 28 months). The risk of arthralgia occurring is 2.9-fold higher in induction/titration phase compared to maintenance phase.

The mean duration of arthralgia was 15 days and ranged 1 day to 936 days; 78% of arthralgia episodes had a duration of less than 14 days, and 1% of arthralgia episodes persisted at least 180 days. Severe

arthralgia (severe pain limiting self-care activities of daily living) was experienced in 14 (5%) patients. Arthralgia episodes were managed with concomitant medicinal products (e.g., nonsteroidal anti-inflammatory drugs, glucocorticoids, and/or antipyretic), dose reduction (4% of episodes), treatment interruption (4% of episodes), or treatment withdrawal (0.6% of episodes), and 97% of arthralgia episodes resolved by the time of the data cut-off.

Persistent arthralgia (lasting at least 6 months) occurred in 19 (7%) patients with a total of 24 episodes. Persistent arthralgia occurred as early as 6 days and up to 1526 days into Palynziq treatment (median: 554 days from Palynziq treatment initiation). Dose was not changed for 23 (96%) episodes and dose was reduced for 1 (4%) episode. All persistent arthralgia episodes resolved without sequelae.

Injection site reactions
Injection site reactions were reported in 266 out of 285 (93%) 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. Injection site reactions were most frequent during induction and titration phase (90% of patients; 3899 episodes over mean treatment duration of 12 months) and decreased in maintenance phase (64% of patients; 1110 episodes over mean treatment duration of 28 months). The risk of injection site reactions occurring is 4.9-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 ranged 1 day to 970 days; 91% of injection site reactions had a duration of less than 14 days, 0.8% of injection site reactions persisted at least 180 days, and 99% of injection site reactions resolved by the time of the data cut-off.

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, 133 out of 285 (47%) patients treated with Palynziq experienced cutaneous reactions (not limited to the injection site) lasting at least 14 days. Cutaneous reactions lasting at least 14 days were most frequent during induction and titration phase (31% of patients; 137 episodes over mean treatment duration of 12 months) and decreased in maintenance phase (38% of patients; 129 episodes over mean treatment duration of 28 months). 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 (37 patients; 13%), rash (33 patients; 12%), erythema (15 patients; 5%), and urticaria (15 patients; 5%). Other reactions reported included skin exfoliation, generalised rash, erythematous rash, maculo-papular rash, and pruritic rash. The mean (SD) time from first dose of pegvaliase to onset was 372 (384) days. The mean (SD) duration of these reactions was 64 (78) days, and the maximum duration was 638 days, 5% of these reactions persisted at least 180 days, and 86% of these reactions resolved by the time of the data cut-off.

Immunogenicity

All patients treated with Palynziq developed a sustained total anti-pegvaliase antibody (TAb) response with a majority of patients (91%) becoming positive by Week 4. Mean TAb titres peaked 2 weeks after initiation of pegvaliase and then were sustained through long-term treatment (greater than 1 year after treatment initiation). Anti-phenylalanine ammonia lyase (PAL) IgM was detected in all patients with a majority of treated patients (98%) becoming positive by 2 months. Anti-PAL IgG was detected in almost all patients by 4 months. Mean anti-PAL (IgM and IgG) titres peaked 3 to 6 months post

treatment initiation and were relatively stable through long-term treatment (greater than 1 year after pegvaliase initiation). Pegvaliase induced anti-PEG IgM and IgG responses were detected in the majority of patients (98%) and titres peaked at 1 to 3 months after treatment initiation and then returned to baseline levels in most patients by 6 to 9 months after treatment initiation (see section 4.5). Neutralising antibodies (NAb) capable of inhibiting PAL enzyme activity were detected in a majority of patients over time with 78% of patients testing positive for NAb at one year after treatment initiation and maintaining stable NAb titres 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 returned towards baseline. Presence of antibody titres were 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). 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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

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 and 4.8.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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.

Mechanism of action

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

Clinical efficacy and safety

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 301: Treatment initiation (Induction and Titration)
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 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: Efficacy assessment
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.

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.

Overall treatment experience from Study 301 and Study 302
At the time of the data cut-off, 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, 164 patients received treatment for at least 2 years, 2 patients continued treatment but had not yet reached 2 years of treatment, and 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 345 micromol/l at Month 24 (n=90), and these reductions in mean blood phenylalanine levels were maintained through Month 36 (341 micromol/l; n=48) (see Table 4 and Figure 1). Median change from baseline was -634 micromol/l at Month 12, -965 micromol/l at Month 24, and -913 micromol/l at Month 36.

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=160; a reduction of 5.9) and Month 36 (n=92; a reduction of 6.7). 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=45; a reduction of 10.6).

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=117; a reduction of 2.2) and Month 36 (n=51; 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), and Month 24 (14 g increase from baseline) and Month 36 (25 g increase from baseline).

Figure 1: Mean (SE) phenylalanine levels over time

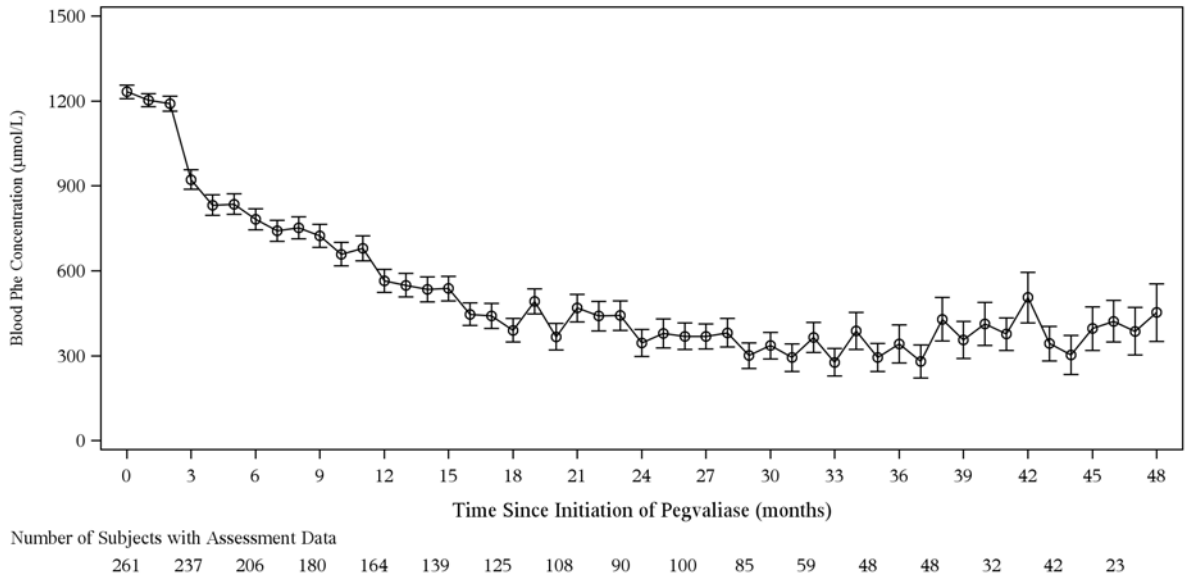


Table 4: Efficacy results at Month 12, Month 18, Month 24 and Month 36 in Palynziq-treated patients

	Baseline	Month 12	Month 18	Month 24	Month 36
Blood phenylalanine[1]					
N	261	164[2]	125[2]	90[2]	48[2]
Mean (SD) blood phenylalanine (micromol/l)	1233 (386)	565 (531)	390 (469)	345 (453)	341 (465)
Change from baseline (micromol/l) Mean (SD) Median	-	 -662 (588) -634	 -883 (565) -920	 -873 (566) -965	 -956 (536) -913
ADHD inattention[3] subscale (investigator-rated)					
N	253	178	175	167	97
Mean (SD) inattention score	9.8 (6.1)	5 (4.9)	4.6 (4.7)	4.2 (4.6)	3.7 (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=160 -5.9 (6.1) -5	n=92 -6.7 (6.4) -5.5
ADHD inattention[3] subscale (investigator-rated) with baseline score > 9					
N	116	80	78	76	45
Mean (SD) inattention score	15.3 (4.1)	7.6 (4.9)	6.6 (5)	5.9 (4.9)	5.1 (5.6)
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=45 -10.6 (6.4) -12
PKU-POMS confusion[3] subscale (self-rated)					
N	170	181	178	169	100
Mean (SD) confusion score	4 (2.7)	2.4 (2.1)	2.1 (2.2)	2 (2.1)	1.8 (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=117 -2.2 (2.7) -2	n=51 -2.2 (3.1) -2
Protein intake from intact food (g)					
N	250	160	111	84	46
Mean (SD)	39 (28)	47 (29)	50 (27)	54 (27)	72 (27)
Change from baseline protein intake (n)[4] Mean (SD) Median	-	n=154 9 (25) 4	n=106 12 (25) 9	n=81 16 (28) 14	n=44 27 (34) 25

[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.

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 66% of patients reached blood phenylalanine level ≤ 360 micromol/l by 12 months, 24 months, and 36 months, respectively.

Impact 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.

The European Medicines Agency has deferred the obligation to submit the results of studies with Palynziq in one or more subsets of the paediatric population for the treatment of hyperphenylalaninaemia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Pegvaliase is a PEGylated recombinant phenylalanine ammonia lyase (rAvPAL), derived from the cyanobacterium *Anabaena variablis* 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). 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.

Biotransformation

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.

Elimination

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).

5.3 Preclinical safety data

Dose-dependent reductions in body weight gain attributed to decreased plasma phenylalanine levels to below normal levels in normal animals (monkeys, rats and rabbits) was observed in single and repeat dose toxicology studies as well as developmental and reproductive toxicity studies with pegvaliase. Decreased plasma phenylalanine and reduced body weight gain was reversible after cessation of treatment.

In cynomolgus monkeys, the incidence and severity of arterial inflammation was dose dependent and observed in a wide range of organs and tissues at clinically relevant exposures in the 4- and 39-week repeat-dose toxicology studies. The arterial inflammation observed in these studies involved small arteries and arterioles in a wide range of organs and tissues and in subcutaneous injection sites. Arteritis was attributed to the immune-mediated response associated with chronic administration of foreign protein to the animals. The vascular inflammation observed in these studies was reversible upon cessation of treatment.

In rats, dose dependent vacuolation attributed to pegvaliase treatment was observed at clinically relevant exposures in the 4- and 26-week repeat-dose toxicity studies in rats in multiple organs and tissues, but not in cynomolgus monkeys. No vacuolation was observed in the brain. Vacuoles in all tissues, with the exception of the kidney, resolved or were diminished by the end of the recovery period, suggesting partial reversibility. The vacuolation observed in these studies was not associated with any organ related toxicities as determined by clinical chemistry/urinalysis and histopathological analysis. The clinical significance of these findings and functional consequences are unknown.

Adverse reproductive and developmental effects of pegvaliase in rats and rabbits were dose dependent and included reduced implantation rate, smaller litter size, lower foetal weights, and increased foetal alterations. Additional findings in rabbits included increased abortions, foetal malformations and embryo/foetal lethality. These findings occurred in the presence of maternal toxicity (decreased body weights, decreased ovarian weights, and decreased food consumption) and were associated with

markedly decreased maternal blood phenylalanine below normal levels in non-PKU animals. The contribution of maternal phenylalanine depletion to the incidence of embryo-foetal developmental effects was not evaluated.

In the peri/postnatal study, pegvaliase 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. The effects in offspring were associated with maternal toxicity.

Long-term studies in animals to evaluate carcinogenic potential or studies to evaluate mutagenic potential have not been performed with pegvaliase. Based on its mechanism of action, pegvaliase is not expected to be tumorigenic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trometamol
Trometamol hydrochloride
Sodium chloride
trans-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

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.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze.

See section 6.3 for additional information on storage outside the refrigerator (below 25°C).

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. After injection, the spring expands causing the needle to be covered by the needle guard.

<u>Pre-filled syringe 2.5 mg (white plunger):</u>
Each carton contains 1 pre-filled syringe.

<u>Pre-filled syringe 10 mg (green plunger):</u>
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 and other handling

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.

7. MARKETING AUTHORISATION HOLDER

BioMarin International Limited
Shanbally, Ringaskiddy
County Cork
Ireland
P43 R298

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1362/001 1 x 2.5 mg pre-filled syringe
EU/1/19/1362/002 1 x 10 mg pre-filled syringe
EU/1/19/1362/003 1 x 20 mg pre-filled syringe
EU/1/19/1362/004 10 x 20 mg pre-filled syringes

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}

10. DATE OF REVISION OF THE TEXT

MM/YYYY

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

BioMarin Pharmaceutical Inc.
Galli Drive Facility
46 Galli Drive
Novato
CA 94949
United States

Name and address of the manufacturer(s) responsible for batch release

BioMarin International Limited
Shanbally, Ringaskiddy
County Cork
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted to medical prescription. (see Annex I: Summary of Product Characteristics, section 4.2)

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of Palynziq in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where Palynziq is marketed, all healthcare professionals and patients, carers and observers who are expected to prescribe, use or oversee the administration of Palynziq have access to/are provided with the following educational package:

- Physician educational material
- Patient information pack

- **The physician educational material** should contain:
  - The Summary of Product Characteristics
  - Guide for healthcare professionals

- **The Guide for healthcare professionals** shall contain the following key elements:
  - Information on the risk of acute systemic hypersensitivity reactions and details of the risk minimisation measures necessary to minimise this risk (i.e. premedication, trained observer, prescription of adrenaline injection device).
  - Management of acute systemic hypersensitivity reactions and information on retreatment
  - Key messages that must be conveyed and elements that must be addressed prior to self-injection by the patient, in particular:
    - training of patients to recognise the signs and symptoms of acute systemic hypersensitivity reactions and the action to be taken if such a reaction occurs
    - prescription of adrenaline injection device and training on its use
    - premedication requirements
    - provision of appropriate instruction on self-administration of pegvaliase
    - assessment of competency in self-injection by patient
    - requirement for a trained observer for at least the first 6 months of treatment
    - training of the observer to recognise the signs and symptoms of acute systemic hypersensitivity reactions, to seek immediate medical care if a reaction occurs, and how to properly administer adrenaline injection device
    - provision of the guide for patients and trained observers and patient alert card
  - Information about the observational study to evaluate long term safety and the importance of contributing to such a study where applicable

- **The patient information pack** should contain:
  - The patient information leaflet
  - The guide for patients and trained observers
  - The patient alert card

- **The guide for patients and trained observers** shall contain the following key messages:
  - Description of the signs and symptoms of severe allergic reactions
  - Information on the action to be taken by the patient and/or trained observer in the event of the occurrence of a severe allergic reaction
  - Description of the risk minimisation measures necessary to minimise the risk of severe allergic reactions, in particular:
    - Premedication requirements
    - Requirement to carry adrenaline injection device at all times
    - Requirement for trained observer for at least the first 6 months of treatment
  - The need to contact the prescriber in the event of a severe allergic reaction prior to continuing treatment

- The importance of carrying the patient alert card

- **The patient alert card** shall contain the following key messages:
  - A warning message for HCPs treating the patient at any time, that the patient is using Palynziq and severe allergic reactions have been associated with this product
  - Signs or symptoms of the severe allergic reactions and action to be taken in the event of such a reaction
  - The importance of carrying an adrenaline injection device and the patient alert card at all times
  - Emergency contact details for the patient and contact details of the prescriber

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

2.5 MG CARTON

1. NAME OF THE MEDICINAL PRODUCT

Palynziq 2.5 mg solution for injection in pre-filled syringe
pegvaliase

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Excipients: trometamol, trometamol hydrochloride, sodium chloride, *trans*-cinnamic acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

Can be stored outside the refrigerator (below 25°C) for a single period up to 30 days.

Date removed from refrigeration: _____/_____/_____

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioMarin International Limited
Shanbally, Ringaskiddy
County Cork
Ireland
P43 R298

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1362/001 2.5 mg pre-filled syringe

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Palynziq 2.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

10 MG CARTON

1. NAME OF THE MEDICINAL PRODUCT

Palynziq 10 mg solution for injection in pre-filled syringe
pegvaliase

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Excipients: trometamol, trometamol hydrochloride, sodium chloride, *trans*-cinnamic acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

Can be stored outside the refrigerator (below 25°C) for a single period up to 30 days.

Date removed from refrigeration: _____/_____/_____

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioMarin International Limited
Shanbally, Ringaskiddy
County Cork
Ireland
P43 R298

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1362/002 10 mg pre-filled syringe

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Palynziq 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

20 MG CARTON

1. NAME OF THE MEDICINAL PRODUCT

Palynziq 20 mg solution for injection in pre-filled syringe
pegvaliase

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Excipients: trometamol, trometamol hydrochloride, sodium chloride, *trans*-cinnamic acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled syringe
10 pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

Can be stored outside the refrigerator (below 25°C) for a single period up to 30 days.

Date removed from refrigeration: _____/_____/_____

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioMarin International Limited
Shanbally, Ringaskiddy
County Cork
Ireland
P43 R298

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1362/003 1 x 20 mg pre-filled syringe
EU/1/19/1362/004 10 x 20 mg pre-filled syringes

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Palynziq 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

2.5 MG TRAY COVER

1. NAME OF THE MEDICINAL PRODUCT

Palynziq 2.5 mg solution for injection in pre-filled syringe
pegvaliase

2. NAME OF THE MARKETING AUTHORISATION HOLDER

BioMarin International Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Subcutaneous use

Date removed from refrigeration: _____/_____/_____

Peel here

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

10 MG TRAY COVER

1. NAME OF THE MEDICINAL PRODUCT

Palynziq 10 mg solution for injection in pre-filled syringe
pegvaliase

2. NAME OF THE MARKETING AUTHORISATION HOLDER

BioMarin International Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Subcutaneous use

Date removed from refrigeration: _____/_____/_____

Peel here

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

20 MG TRAY COVER

1. NAME OF THE MEDICINAL PRODUCT

Palynziq 20 mg solution for injection in pre-filled syringe
pegvaliase

2. NAME OF THE MARKETING AUTHORISATION HOLDER

BioMarin International Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Subcutaneous use

Date removed from refrigeration: _____/_____/_____

Peel here

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

2.5 MG PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Palynziq 2.5 mg injection
pegvaliase
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

10 MG PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Palynziq 10 mg injection
pegvaliase
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

20 MG PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Palynziq 20 mg injection
pegvaliase
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Palynziq 2.5 mg solution for injection in pre-filled syringe
Palynziq 10 mg solution for injection in pre-filled syringe
Palynziq 20 mg solution for injection in pre-filled syringe
pegvaliase

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Palynziq is and what it is used for

Palynziq contains the active substance pegvaliase, an enzyme that can break down a substance called phenylalanine in the body. Palynziq is a treatment for patients aged 16 years and older with phenylketonuria (PKU), a rare inherited disorder that causes phenylalanine from proteins in food to build up in the body. People who have PKU have high levels of phenylalanine and this can lead to serious health problems. Palynziq reduces the levels of phenylalanine in the blood of patients who have PKU whose blood phenylalanine levels cannot be kept below 600 micromol/l by other means such as by diet.

2. What you need to know before you use Palynziq

Do not use Palynziq

- if you have a severe allergy to pegvaliase or any other ingredients of this medicine, or another medicine that contains polyethylene glycol (PEG) (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist, or nurse before using Palynziq.

Allergic reactions
You may have allergic reactions when being treated with Palynziq. Your doctor will tell you how to manage your allergic reactions based on the severity of the reaction, and will prescribe you additional medicines to manage the reaction.

Before using Palynziq, tell your doctor if you cannot use or do not want to use an adrenaline injection device to treat a severe allergic reaction to Palynziq.

Palynziq can cause severe allergic reactions that may be life-threatening and these can happen any time after a Palynziq injection.

- ***Stop injecting Palynziq if any of the following symptoms occur.***

  - Swelling of the face, eyes, lips, mouth, throat, tongue, hands and/or feet
  - Trouble breathing or wheezing
  - Throat tightness or choking feeling
  - Trouble swallowing or speaking
  - Feeling dizzy or fainting
  - Losing control of urine or stools
  - Rapid heartbeat
  - Hives (like an itchy, bumpy skin rash) that spreads quickly
  - Flushing
  - Severe stomach cramps or pain, vomiting, or diarrhoea

- ***Use adrenaline injection device as instructed by your doctor and seek urgent medical assistance.***

Your doctor will prescribe an adrenaline injection device to use for a severe allergic reaction. Your doctor will train you and someone helping you on when and how to use adrenaline. Keep the adrenaline injection device with you at all times.

For at least the first 6 months of treatment, someone must be with you when you are self-injecting Palynziq. This person must stay with you for at least 1 hour after your injection to watch you for signs and symptoms of a severe allergic reaction and, if needed, give you an injection of adrenaline and call for emergency medical help.

If you have a severe allergic reaction, do not continue to use Palynziq until you have talked with the doctor who prescribes you Palynziq. Tell your doctor that you had a severe allergic reaction. Your doctor will tell you if you can continue Palynziq treatment.

Time needed to lower your blood phenylalanine levels
Your doctor will start you on Palynziq at a low dose and will increase your dose slowly. It will take time to find the dose that works best to lower your blood phenylalanine levels. Most people respond within 18 months, but it can sometimes take up to 30 months.

Injection of other medicines that contain PEG while using Palynziq
Palynziq includes an ingredient called polyethylene glycol (PEG). If you inject Palynziq with another injectable medicine that contains PEG, such as PEGylated medroxyprogesterone acetate, you may have an allergic reaction. Tell your doctor or pharmacist if you are injecting, have recently injected or might inject any other medicines.

Blood phenylalanine levels that are too low
You may have blood phenylalanine levels that are too low when using Palynziq. Your doctor will check your blood phenylalanine levels monthly. If your blood phenylalanine levels are too low, your doctor may ask you to change your diet and/or will lower your dose of Palynziq. Your doctor will check your blood phenylalanine levels every 2 weeks until your blood phenylalanine levels return to normal.

Children and adolescents
It is not known if Palynziq is safe and effective in children and adolescents less than 16 years of age with PKU and therefore should not be used in people aged less than 16 years.

Other medicines and Palynziq
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

Palynziq is not recommended during pregnancy unless your condition requires treatment with Palynziq and other ways of controlling your blood phenylalanine levels do not work. If your phenylalanine levels are too high or too low during pregnancy, this may harm you or your baby. You and your doctor will decide the best way for you to manage your blood phenylalanine levels. It is very important to keep your phenylalanine levels under control before and during pregnancy.

It is not known if Palynziq passes into breast milk or if it will affect your baby. Talk to your healthcare provider about the best way to feed your baby if you use Palynziq.

It is not known if Palynziq has an effect on fertility. Animal studies suggest that women may have difficulty becoming pregnant if their phenylalanine levels are abnormally low.

Driving and using machines
Palynziq can affect your ability to drive and use machines if you have a severe allergic reaction.

Palynziq contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per pre-filled syringe, that is to say essentially ‘sodium-free’.

3. How to use Palynziq

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Palynziq is given as an injection under the skin (subcutaneous injection).

Dose

- You will start Palynziq at the lowest dose. You will use the 2.5 mg syringe once a week for at least the first 4 weeks. The 2.5 mg syringe has a white plunger.
- Your doctor will then slowly increase your dose and/or how often you inject Palynziq. Your doctor will tell you how long to stay at each dose. Slowly increasing your dose over time allows your body to adjust to this medicine.
- The goal is to reach a daily dose that lowers your blood phenylalanine levels to within the target range of 120 to 600 micromol/l and does not cause too many side effects. Patients usually need a daily dose of 20 mg, 40 mg, or 60 mg to reach their target blood phenylalanine level.

Example of steps to reach your blood phenylalanine goal

Palynziq dose and how often to take it	Syringe colour
2.5 mg once a week	White plunger
2.5 mg two times a week	
10 mg once a week	Green plunger
10 mg twice a week	
10 mg four times a week	
10 mg daily	
20 mg daily	Blue plunger
40 mg daily (2 injections of 20 mg pre-filled syringe)[1]	
60 mg daily (3 injections of 20 mg pre-filled syringe)[1]	

[1] If you need more than one injection to receive your daily dose, all injections should be done at the same time of day and injection sites should be at least 5 centimetres away from each other. Do not divide your daily dose throughout the day.

- Your doctor will continue to check your blood phenylalanine levels during treatment and may adjust your dose of Palynziq or ask you to change your diet.
- Your doctor will need to check your blood phenylalanine monthly to see if this medicine is working for you.

Starting Palynziq

- Your healthcare provider will give you the Palynziq injection until you (or a caregiver) can do it yourself.
- Your doctor will prescribe medicines for you to take before your Palynziq injection, such as paracetamol, fexofenadine, and/or ranitidine. These medicines help to reduce the symptoms of an allergic reaction.
- A healthcare provider will monitor you for at least 1 hour after you get Palynziq for signs and symptoms of an allergic reaction.
- Your doctor will also prescribe adrenaline injection device to use for any severe allergic reactions. Your healthcare provider will also tell you which signs and symptoms to look out for and what to do if you have a severe allergic reaction.
- Your doctor will show you how and when to use the adrenaline injection device. Keep it with you at all times.

Continuing Palynziq

- This medicine comes in pre-filled syringes with 3 different strengths (2.5 mg-white plunger, 10 mg-green plunger, or 20 mg-blue plunger). You may need more than one pre-filled syringe for your prescribed dose. Your healthcare provider will tell you which syringe, or a combination of syringes, to use and will show you (or a caregiver) how to inject Palynziq.
- The “Instructions for Use” (section 7 of this leaflet) shows you:
  - how to prepare and inject Palynziq and
  - how to throw away Palynziq syringes properly after you use them
- Your doctor will tell you how long to continue taking medicines such as paracetamol, fexofenadine, and/or ranitidine before you take Palynziq.
- For at least the first 6 months of Palynziq treatment, you must have someone with you when you self-inject Palynziq, and for at least 1 hour after your injection to watch for signs and symptoms of a severe allergic reaction and, if needed, give you an injection of adrenaline and call for emergency medical help.
  - Your doctor will train them on the signs and symptoms of a severe allergic reaction and how to give an injection of adrenaline.

- Your doctor will tell you if you need an observer for longer than 6 months.
- Do not change your protein intake unless your doctor tells you to.

If you use more Palynziq than you should
If you use more Palynziq than you should, tell your doctor. See section 4 for details on what to do based on your symptoms.

If you forget to use Palynziq
If you miss a dose, take your next dose at the regular time. Do not take two doses of Palynziq to make up for a missed dose.

If you stop taking Palynziq
If you stop taking Palynziq treatment, your blood phenylalanine levels are likely to increase. Talk to your doctor before stopping Palynziq treatment.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Allergic reactions occur very commonly (*may affect more than 1 in 10 people)* and range in severity. Symptoms of allergic reaction can include skin rash, itching, swelling of head or face, itchy or runny eyes, cough, and wheezing. Your doctor will tell you how to manage any allergic reactions based on their severity, and will prescribe you additional medicines to manage the reaction. Some of these allergic reactions can be more serious, as described below, and will require immediate attention.

Serious side effects include:

- Sudden severe allergic reactions: *(Common – may affect up to 1 in 10 people).* Stop injecting Palynziq if you notice any serious sudden signs of allergy or combination of signs listed below.
  - Swelling of the face, eyes, lips, mouth, throat, tongue, hands and/or feet
  - Trouble breathing or wheezing
  - Throat tightness or a choking feeling
  - Trouble swallowing or speaking
  - Feeling dizzy or fainting
  - Losing control of urine or stools
  - Rapid heartbeat
  - Hives (like an itchy, bumpy skin rash) that spreads quickly
  - Flushing
  - Severe stomach cramps or pain, vomiting, or diarrhoea

  Use adrenaline injection device as instructed by your doctor and seek urgent medical assistance. Your doctor will prescribe an adrenaline injection device to use for a severe allergic reaction. Your doctor will train and instruct you and someone helping you on when and how to use adrenaline. Keep the adrenaline injection device with you at all times.

Contact your doctor ***immediately*** if you have the following:
- A type of allergic reaction called serum sickness which includes a combination of fever (high temperature), rash, muscle and joint aches *(Common – may affect up to 1 in 10 people)*

Other side effects

Very common: may affect more than 1 in 10 people
- skin redness, swelling, bruising, tenderness, or pain where you injected Palynziq
- joint pain

- decrease in complement factors C3 and C4 proteins (which are parts of your immune system) in blood test
- allergic reaction
- too low levels of phenylalanine in blood tests
- headache
- skin rash
- stomach pain
- feeling sick, also called nausea
- vomiting
- hives (raised itchy rash on the skin)
- itchiness
- thinning or loss of hair
- cough
- increase in c-reactive protein (CRP) in blood test (CRP is a protein that indicates that you have inflammation)
- swollen glands in the neck, armpit or groin
- skin redness
- muscle pain

Common: may affect up to 1 in 10 people
- joint stiffness
- joint swelling
- muscle stiffness
- skin rash with small bumps
- blistering or peeling of the outer layer of the skin

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Palynziq

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the syringe label, tray cover, and carton after "EXP". The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C). Do not freeze.

If needed, you may store Palynziq in its sealed tray outside the refrigerator (below 25°C) for up to a single period of 30 days away from sources of heat. Record the date removed from refrigeration on the unopened product tray. Once stored outside of refrigeration, the product must not be returned to the refrigerator.

Do not use this medicine if the pre-filled syringe is damaged or you notice the solution is discoloured, cloudy, or if you can see particles.

Use safe disposal procedures for syringes. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Palynziq contains
- The active substance is pegvaliase.
  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 other ingredients are trometamol, trometamol hydrochloride, sodium chloride (see section 2 for further information), *trans*-cinnamic acid, water for injections.

What Palynziq looks like and contents of the pack
Palynziq solution for injection (injection) is a clear to slightly opalescent, colourless to pale yellow solution. The pre-filled syringe includes an automatic needle guard.

Pre-filled syringe 2.5 mg (white plunger):
Each 2.5 mg carton contains 1 pre-filled syringe.

Pre-filled syringe 10 mg (green plunger):
Each 10 mg carton contains 1 pre-filled syringe.

Pre-filled syringe 20 mg (blue plunger):
Each 20 mg carton contains 1 or 10 pre-filled syringes.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
BioMarin International Limited
Shanbally, Ringaskiddy
County Cork
Ireland
P43 R298

This leaflet was last revised in MM/YYYY.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

7. Instructions for use

BEFORE YOU START

Read this Instructions for use before you start using the Palynziq pre-filled syringe and each time you get a new prescription. There may be new information. Also, talk to your healthcare provider about your medical condition or your treatment.

Follow these instructions carefully while you are using Palynziq. If your healthcare provider decides that you or your caregiver can give your injections of Palynziq at home, your healthcare provider will show you or your caregiver how to inject Palynziq before you inject it for the first time. **Do not** inject Palynziq until your healthcare provider has shown you or your caregiver how to inject Palynziq.

Talk to your healthcare provider if you have any questions about how to inject Palynziq the right way.

Do not share your pre-filled syringes with anyone else.

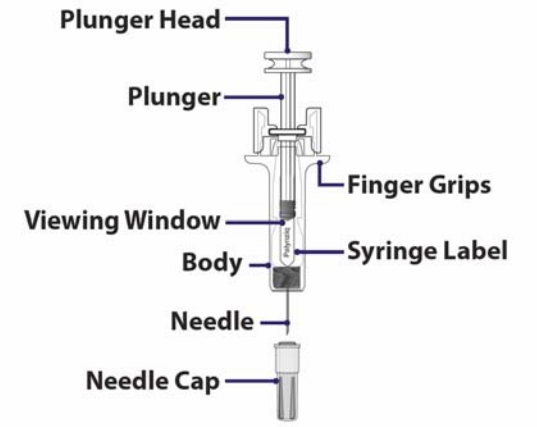
For storage instructions, refer to section 5 "*How to store Palynziq*" of this leaflet.

Important things to know about using your Palynziq pre-filled syringe:

- Use each Palynziq pre-filled syringe once only. **Do not** use a Palynziq syringe more than once.
- **Never** pull back on the plunger.
- **Do not** remove the needle cap until you are ready to inject.

Figure A below shows what the pre-filled syringe looks like before use.

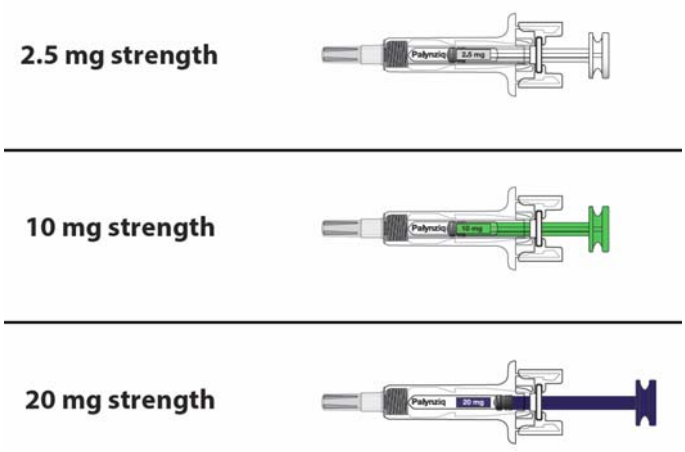
Figure A



Select the correct Palynziq pre-filled syringe(s) for your dose:
When you receive your Palynziq pre-filled syringe(s), check that the name "Palynziq" appears on the carton(s).

- Palynziq pre-filled syringes come in 3 different strengths: 2.5 mg, 10 mg, and 20 mg.
- You may need more than one pre-filled syringe for your prescribed dose. Your healthcare provider will tell you which syringe, or combination of syringes, to use. Ask your healthcare provider if you have any questions.
- Before you inject Palynziq, check each carton and syringe to make sure you have the right pre-filled syringe for your prescribed dose.

Figure B



PREPARING FOR INJECTION

Step 1: Collect supplies:
Gather your supplies for the injection and place them on a clean flat surface. Take out the required number of cartons needed for your dose from the refrigerator.

Supplies you will need for your Palynziq Injection:

- Palynziq pre-filled syringe(s) in sealed tray(s). Each tray contains 1 syringe.
- gauze pad or cotton ball
- 1 alcohol pad
- 1 bandage
- 1 sharps disposal or puncture resistant container

Step 2: Remove Palynziq tray(s) from carton and check expiry date:

- Take out the cartons needed for your dose from the refrigerator. Check the expiry date on the carton. If the expiry date has passed, do not use the pre-filled syringe in that carton.
- Open each carton and take out the sealed tray you need for your dose.
- Place each sealed tray on a clean, flat surface out of reach of children and pets.
- Put the carton with any remaining trays back in the refrigerator. If a refrigerator is not available, see section 5 "*How to store Palynziq*" in this leaflet.

Step 3: Allow Palynziq tray(s) to sit at room temperature for 30 minutes before opening:

Let the sealed tray(s) sit at room temperature for **at least 30 minutes**. Injecting cold Palynziq can be uncomfortable.

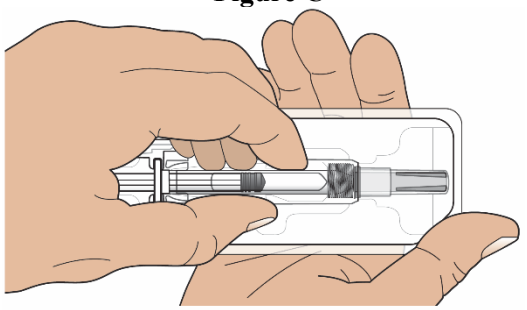
- **Do not** warm up the pre-filled syringe in any other way. **Do not** use a microwave and do not place in hot water.

Step 4: Remove syringe from tray:

Peel the cover from the tray. Hold the middle of the pre-filled syringe body and take out the pre-filled syringe from the tray (see Figure C).

- **Do not** use the pre-filled syringe if it looks damaged or used. Use a new pre-filled syringe for your injection.
- **Do not** remove the needle cap from your pre-filled syringe.
- **Do not** shake or roll the syringe in your hands.

Figure C

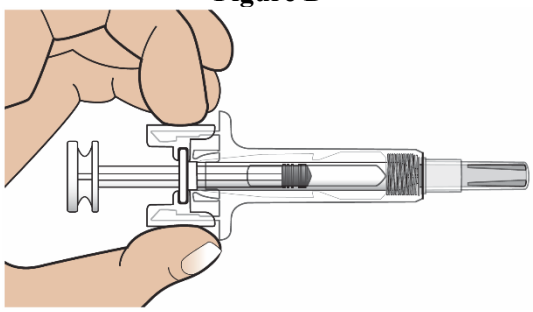


Step 5: Check syringe strength and check for particles:

Check the syringe label to make sure you have the correct strength for your prescribed dose. Look at the liquid through the viewing window (see Figure D). The liquid should look clear and colourless to pale yellow. It is normal to see an air bubble.

- **Do not** flick or try to push the bubble out.
- **Do not** use the pre-filled syringe if the liquid is cloudy, discoloured, or has lumps or particles in it. Use a new pre-filled syringe for your injection.

Figure D



INJECTING PALYNZIQ

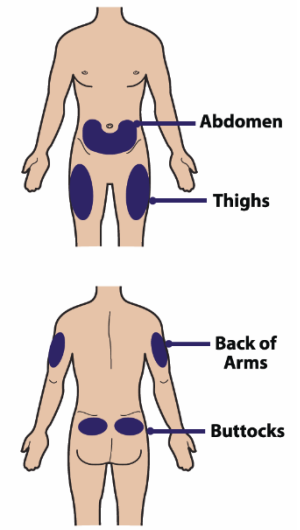
Step 6: Choose your injection site.

The recommended injection sites are:

- Front middle of the thighs.
- Lower part of the abdomen except for the 5 centimetre area around the belly button (navel).

If a caregiver is giving the injection, the top of the buttocks and the back of the upper arms may also be used (see Figure E).

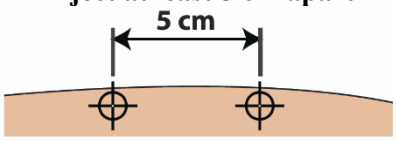
Figure E



Note:

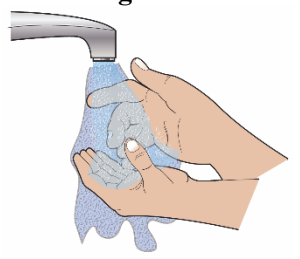
- **Do not** inject into moles, scars, birthmarks, bruises, rashes, or areas where the skin is hard, tender, red, damaged, burned, inflamed, or tattooed.
- If you need more than 1 injection for your daily dose, the injection sites should be at least 5 centimetres away from each other (see Figures E and F).
- Each day, change (rotate) your injection sites. Choose an injection site that is at least 5 centimetres away from the injection site(s) you used the day before. It can be on the same part of the body or a different part of the body (see Figures E and F).

Figure F
Inject at least 5 cm apart



Step 7: Wash your hands well with soap and water (see Figure G).

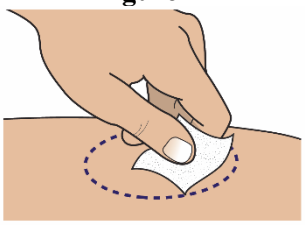
Figure G



Step 8: Clean the chosen site with an alcohol pad. Let the skin air dry for at least 10 seconds before injecting (see Figure H).

- **Do not** touch the cleaned injection site.
- **Do not** remove the needle cap until you are ready to inject Palynziq.
- Before injecting, check to make sure the needle is not damaged or bent.

Figure H

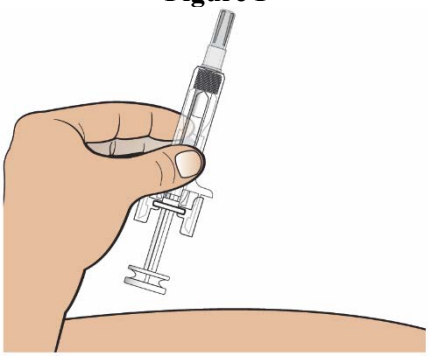


Inject Palynziq

Step 9: Hold the body of the pre-filled syringe with one hand with the needle facing away from you (see Figure I).

- **Do not** use the pre-filled syringe if it has been dropped. Use a new pre-filled syringe for your injection.

Figure I

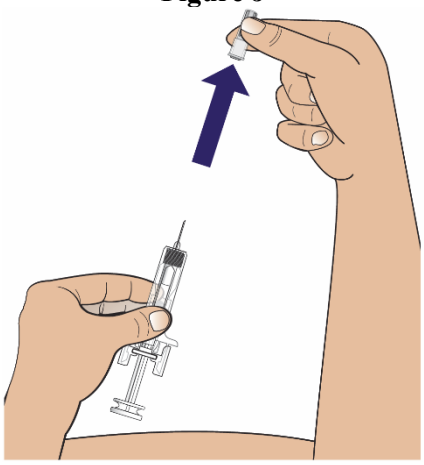


Step 10: Pull the needle cap straight off the needle (see Figure J).

- **Do not** twist the needle cap during removal.
- **Do not** hold the pre-filled syringe by the plunger or plunger head while taking the needle cap off.

You may see a drop of liquid on the tip of the needle. This is normal. **Do not** wipe it away. Throw the needle cap away in a sharps disposal or puncture-resistant container.

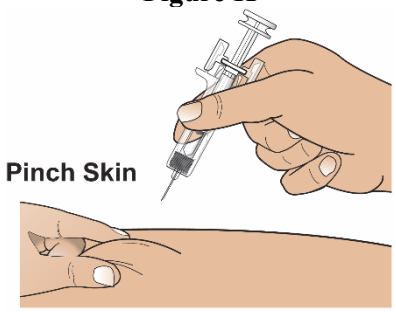
Figure J



Step 11: Hold the body of the pre-filled syringe in 1 hand between your thumb and index finger. Use your other hand to pinch up the skin around the injection site. Hold the skin firmly (see Figure K).

- **Do not** touch the plunger head while inserting the needle into the skin.

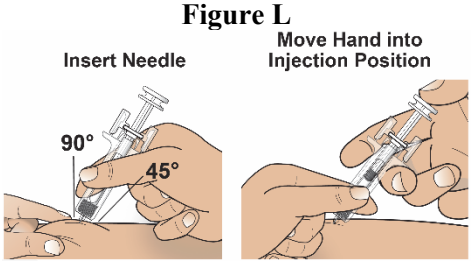
Figure K



Step 12: Use a quick motion to fully insert the needle into the pinched skin at a 45 to 90 degree angle (see Figure L).

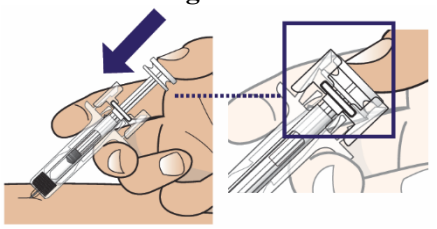
Release the pinch of skin. Use that hand to hold the bottom of the syringe steady. Place the thumb of your other hand on the plunger head (see Figure L).

Figure L



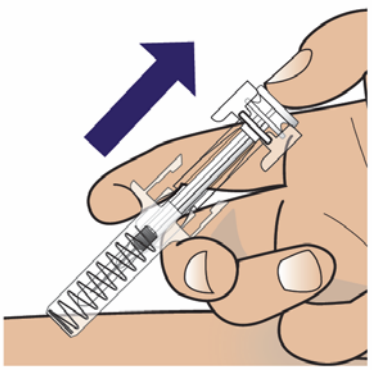
Step 13: Use your thumb to push in the plunger slowly and steadily as far as it will go to inject all the medicine (see Figure M). More pressure may be needed to inject all the medicine for the 10 mg and 20 mg strengths.

Figure M



Step 14: Slowly move your thumb up to release the plunger allowing the needle to automatically be covered by the syringe body (see Figure N).

Figure N



Treat injection site

Step 15: Treat injection site (if needed).

If you see drops of blood at the injection site, press a sterile cotton ball or gauze over the injection site and hold for about 10 seconds. You may cover the injection site with an adhesive bandage if needed.

If more than one syringe is needed:

Step 16: If your health care provider tells you to use more than one syringe for your dose, repeat Steps 4 to 15 listed above for each syringe that you use.

If your dose requires more than one syringe, repeat Steps 4 to 15 immediately for each syringe you use.

- **Note: Do not** inject multiple injections in the same spot. The injection sites should be at least 5 centimetres away from each other. See Step 6 for choosing an injection site.
- If multiple syringes are needed for a single dose, you should inject at the same time of day. Doses should not be divided over the course of the day

AFTER THE INJECTION

Dispose of the used syringes
Put your used needles and syringes in a sharps disposal or puncture-resistant container right away after use. Check with your doctor, pharmacist or nurse about the right way to throw away the container. Use safe disposal procedures for syringes.

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