EUROPEAN UNION (EU) RISK MANAGEMENT PLAN (RMP)

FOR

Palynziq™ (pegvaliase)

Date of Report

25 January 2024

BioMarin Pharmaceutical Inc.

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RMP version to be assessed as part of this application:

RMP Version Number:	4.0
Data Lock Point for this RMP:	23 May 2021
Date of final signoff:	25 January 2024

Rationale for submitting an updated RMP:

The current Palynziq RMP version 4.0 was updated in order to remove the requirement of Additional Monitoring as agreed during the Palynziq 5 year renewal (EMA procedure EMEA/H/C/004744/R/0038).

Summary of significant changes in the RMP:

1. Update of Product Overview to reflect that Additional Monitoring is no longer required.

Other RMP versions under evaluation:

Version number of RMP under evaluation:	Not Applicable
Submitted on:	-
Procedure number:	-

Details of the currently approved RMP:

Version number:	3.2
Approved with procedure:	EMEA/H/C/004744/IB/0027
Date of approval (opinion date):	30 May 2022

The RMP has been reviewed and approved by the marketing authorisation holder/applicant's QPPV and the electronic signature is on file.

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LIST OF ABBREVIATIONS

ACMG	American College of Medical Genetics and Genomics
ADA	Anti-drug antibodies
ADHD	Attention Deficit Hyperactivity Disorder
AE	Adverse Events
ALT	Alanine Aminotransferase
ASHR	Acute Systemic Hypersensitivity Reaction
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BH4	Tetrahydrobiopterin 4
BMI	Body Mass Index
C3	Complement 3
C4	Complement 4
CD4	Cluster of Differentiation 4
CIC	Circulating Immune Complex
CNS	Central Nervous System
CRP	C-reactive Protein
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
EC	European Commission
ECG	Electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ESPKU	European Society for Phenylketonuria and Allied Disorders
ETP	Early Treatment Phase
EU	European Union
FDA	Food and Drug Administration
FGR	Foetal Growth Retardation
FPI	First Patient In
H1	Histamine 1 receptor
H2	Histamine 2 receptor
HAE	Hypersensitivity Adverse Events
HCP	Healthcare Provider
HPA	Hyperphenylalaninemia
ICH	International Conference on Harmonisation
IgA	Immunoglobulin A
IgE	Immunoglobulin E

IgG	Immunoglobulin G
IgM	Immunoglobulin M
INN	International Nonproprietary Name
IQ	Intelligence Quotient
ISR	Injection Site Reactions
I/T/M	Induction/Titration/Maintenance
LPO	Last Patient Out
LTP	Late Treatment Phase
MCM	Major Congenital Malformation
MD	Multiple dose
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	Millimetre of mercury
MNT	Medical Nutritional Therapy
NIAID/FAAN	National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network
NIH	National Institutes of Health
NO	Nitric Oxide
NOAEL	No-observed-adverse-effect-level
NHS-MPEG	N-hydroxysuccinimide methoxypolyethylene glycol
PAH	Phenylalanine Hydroxylase
PAL	Phenylalanine Ammonia Lyase
PD	Pharmacodynamic
PEG	Polyethylene Glycol
PL	Patient Leaflet
PK	Pharmacokinetics
PKU	Phenylketonuria
PPI	Proton Pump Inhibitor
PSUR	Periodic Safety Update Report
PT	Preferred term
QPPV	Qualified Person for Pharmacovigilance
QT	Time between the start of the Q wave and the end of the T wave on an ECG
QTc	Corrected QT interval
rAvPAL-PEG	Recombinant *Anabaena variabilis* phenylalanine ammonia lyase - polyethylene glycol
RMP	Risk Management Plan
SC	Subcutaneous
SD	Standard Deviation
SGA	Small for Gestational Age
SmPC	Summary of Product Characteristics

SMQ	Standardised MedDRA query
SpO_2	Peripheral oxygen saturation
TBC	To be completed
TK	Toxicokinetics
ULN	Upper Limit Normal
US/USA	United States/United States of America

PART I: PRODUCT OVERVIEW

Active substance (International Nonproprietary Name [INN] or common name)	Pegvaliase
Pharmacotherapeutic group(s) (Anatomical Therapeutic Chemical [ATC] Code)	A16A
Marketing Authorisation Holder (or Applicant)	BioMarin International Limited Shanbally, Ringaskiddy County Cork Ireland
Number of medicinal product(s) to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Palynziq
Marketing authorisation procedure	Centralised
Brief description of the product including: • **Chemical class** • **Summary of mode of action** • **Important information about its composition**	Polyethylene glycol (PEG)ylated recombinant phenylalanine ammonia lyase, (PAL) or recombinant *Anabaena variabilis* PAL (rAvPAL-PEG).
	Pegvaliase is a PAL enzyme that converts phenylalanine to ammonia and *trans*-cinnamic acid that are metabolised by the liver and excreted in the urine, respectively. It substitutes for the deficient phenylalanine hydroxylase (PAH) enzyme activity and reduces blood phenylalanine levels in the body.
	Pegvaliase is a covalent conjugate of rAvPAL derived from the cyanobacterium *Anabaena variabilis* which is expressed in *E. coli* and conjugated with N-hydroxysuccinimide-methoxypolyethylene glycol (NHS-MPEG), forming the active drug substance pegvaliase (rAvPAL-PEG).
Hyperlink to the product information	Module 1.3.1
Indication(s) in the EEA Current (if applicable)	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 µmol/L) despite prior management with available treatment options.

<table>
<tr><td>Dose in the EEA</td><td></td></tr>
<tr><td>Current</td><td>
Induction

The recommended starting dose for Palynziq is 2.5 mg administered once per week for the first 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 µmol/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 and 600 µmol/L) taking into account patient tolerability, dietary protein intake (see Table 1).

Table 1: Recommended titrating dosing regimen
<table>
<tr><th></th><th>Dose[1] administered subcutaneously</th><th>Duration prior to next dose increase</th></tr>
<tr><td>Induction</td><td>2.5 mg once weekly</td><td>4 weeks[2]</td></tr>
<tr><td rowspan="5">Titration</td><td>2.5 mg twice weekly</td><td>1 week[2]</td></tr>
<tr><td>10 mg once weekly</td><td>1 week[2]</td></tr>
<tr><td>10 mg twice weekly</td><td>1 week[2]</td></tr>
<tr><td>10 mg four times a week</td><td>1 week[2]</td></tr>
<tr><td>10 mg daily</td><td>1 week[2]</td></tr>
<tr><td rowspan="3">Maintenance[3]</td><td>20 mg daily</td><td>12 weeks to 24 weeks[2]</td></tr>
<tr><td>40 mg daily (2 consecutive injections of 20 mg pre-filled syringe)[4]</td><td>16 weeks[2]</td></tr>
<tr><td>60 mg daily (3 consecutive injections of 20 mg pre-filled syringe)[4]</td><td>Maximum recommended dose</td></tr>
</table>
[1] If blood phenylalanine levels are below 30 µmol/L, dietary protein intake should be increased to appropriate levels, and then, if needed, the dose of Palynziq should be reduced.
</td></tr>
</table>

	[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 µmol/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. *Dose adjustments* During titration and maintenance of Palynziq treatment, patients may develop blood phenylalanine levels below 30 µmol/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. Patients should be monitored every 2 weeks until blood phenylalanine levels are within a clinically acceptable range. If hypophenylalaninaemia develops prior to reaching daily dosing, the dose may be reduced to the previous titration dosage. 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.
Pharmaceutical form(s) and strengths	
Current (if applicable)	Solution for injection (injection). Colourless to pale yellow, clear to slightly opalescent solution with pH 6.6-7.4. Each 2.5 mg pre-filled syringe contains 2.5 mg pegvaliase in 0.5 ml solution. Osmolality 260 – 290 mOsm/kg. Each 10 mg pre-filled syringe contains 10 mg pegvaliase in 0.5 ml solution. Osmolality 285 – 315 mOsm/kg, viscous solution. Each 20 mg pre-filled syringe contains 20 mg pegvaliase in 1 ml solution. Osmolality 285 – 315 mOsm/kg, viscous 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.
Is/will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

Module SI: Epidemiology of the indication and target population

Overview

Phenylketonuria (PKU) is a serious, inherited, autosomal recessive metabolic disorder characterised by a deficiency of the liver enzyme, phenylalanine hydroxylase (PAH), in which phenylalanine accumulates to abnormally elevated concentrations in the blood. The high blood phenylalanine levels are toxic to the brain, resulting in significant negative effects on neurocognitive, neuropsychological and executive function performance in adults with PKU. PAH is most abundant in the liver and catalyses the hydroxylation of phenylalanine to tyrosine in the presence of the cofactor tetrahydrobiopterin 4 (BH4).

In adults with PKU, mean blood phenylalanine levels was reported to be 1,179 µmol/L, which is consistent with poor metabolic control despite current treatment (PKU Systematic Review and Meta-Analysis).

Currently, there are two treatment options available for patients with PKU;

- Phenylalanine restriction with medical nutritional therapy (MNT).
- Sapropterin dihydrochloride (Kuvan®) as adjunct to phenylalanine restriction and MNT.

Most PKU patients require lifelong stringent phenylalanine restriction with MNT to control blood phenylalanine levels and to help prevent complications associated with high phenylalanine levels in the brain. However, there are significant challenges associated with the use of MNT over the long term (PKU Systematic Review and Meta-Analysis), and sapropterin is only effective in a small subset (~ 30 %) of PKU subjects with residual PAH activity. Uncontrolled blood phenylalanine in adulthood is associated with impairment of neuropsychiatric, neurocognitive and executive function, a heterogeneous variety of behavioural and psychiatric problems including depression and anxiety, and negatively affects patient quality of life (Moyle, 2007; Pietz, 1997; Smith, 2000; Waisbren, 1999; Gassio, 2003). High blood phenylalanine levels also negatively affect mood and ability to sustain attention in adults with PKU (ten Hoedt, 2010). Several interventional studies have shown improvements on neuropsychiatric and executive function domains when blood phenylalanine levels are controlled in adult PKU patients (Bilder, 2016). These findings suggest that neuropsychiatric and executive functioning deficits are reversible in adults with PKU. Other recently published studies have reported widespread correlations between cognitive performance in adults with PKU and control of hyperphenylalaninemia (HPA) during their life span suggesting that it is important to maintain low blood phenylalanine throughout life (Palermo, 2017; Romani, 2017), in order to provide optimal neurocognitive function.

European guidelines for the management of PKU recommend treatment target phenylalanine levels of≤600 µmol/L for patients older than 12 years (van Wegberg 2017). Similarly, the American College of Medical Genetics and Genomics (ACMG) practice guidelines recommend lifelong management of PKU, with a goal of maintaining blood phenylalanine concentrations≤360 µmol/L (Vockley, 2014).

BioMarin has developed pegvaliase, a genetically modified PAL, an enzyme product of the cyanobacterium *Anabaena variabilis* that is PEGylated to decrease immunogenicity and increase half-life, as a novel treatment for PKU.

Indication

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 µmol/L) despite prior management with available treatment options.

Incidence

Given that PKU is a genetic condition, present throughout life, and patients have a normal life span, the incidence rates are essentially the same as the prevalence rates.

The variability in epidemiological rates of PKU incidence is greater within the European Union (EU) (0.1 to 2.2:10,000) (Loeber, 2007; Guldberg, 1995) than it is between the EU and the United States (US) (1 versus 0.67:10,000) (van Spronsen, 2017; NIHCDP, 2001).

Demographics of the population in the authorised/proposed indication (age, gender, racial and/or ethnic origin) and risk factors for the disease:

PKU is an autosomal recessive condition that theoretically affects males and females equally, and prognosis does not vary with gender.

The main risk factor for the disease is consanguinity. For a given gene-defect, race and ethnicity do not affect the phenotypic expression of the disease as measured by phenylalanine tolerance (the amount of phenylalanine that can be consumed while maintaining normal phenylalanine levels).

The main impact of race and ethnicity is on the nature of the genetic defect. Hundreds of different genetic defects can give rise to the PKU phenotype. These range from those with no PAH activity, low phenylalanine tolerance and a severe disease to those with genetic defects where PAH activity is modestly impaired, phenylalanine tolerance is high resulting in a milder disease. In addition, the phenotype can be associated with reduced or absent PAH activity due to its co-enzyme BH4.

According to an online survey from 81 healthcare providers in 24 European countries, patients with the more severe form of PKU (with untreated blood phenylalanine levels of >1,200 µmol/L) represent 66% of adults with PKU (Trefz, 2015).

This condition is an inherited condition and there are no known additional risk factors.

Main existing treatment options:

The aim of PKU management is to identify patients at birth, to control their HPA long-term in order that they retain and maintain neurological health and neurocognitive function as adults. Though various country-specific guidelines have been developed over the last few years, the first consensus pan-European PKU guidelines were published in 2017 (van Spronsen, 2017). These guidelines for the diagnosis and treatment of PKU were developed by 19 medical specialists in the field throughout Europe under the auspices of the European Society for Phenylketonuria and Allied Disorders (ESPKU).

There are two recommendations pertinent to the treatment of adults with PKU:

- Lifelong treatment is recommended for any patient with PKU whose blood phenylalanine levels are greater than 600 µmol/L; all adults with PKU should have lifelong, systematic follow up in specialised metabolic centres due to specific risks which may occur during adulthood.
- In treated PKU patients aged >12 years (non-pregnant), the target phenylalanine levels are 120 to 600 µmol/L.

Phenylalanine is one of 8 essential amino acids that cannot be synthesized *de novo* in the human body. Thus, in the general population, physiological requirements for phenylalanine are met exclusively by dietary protein intake.

Therefore, patients with PKU must primarily control their blood phenylalanine levels by controlling their dietary phenylalanine intake through the following methods, referred to as MNT:

- Severe natural protein restriction according to individual phenylalanine tolerance
- Low protein phenylalanine -free synthetic food to meet energy requirements
- Phenylalanine -free L-amino acid supplements (e.g. tyrosine, vitamins, or minerals) to correct dietary deficiencies that can result from phenylalanine restriction and reliance on nutritionally incomplete medical foods.

Currently there are two treatment options in Europe for adults with PKU:

- MNT
- MNT in conjunction with treatment with sapropterin

To be optimally effective, MNT needs to be started immediately after birth and continued for life. Stringent and onerous restriction of phenylalanine intake thus prohibits consumption of most natural protein, such as meat, fish, chicken, eggs, nuts, beans, and dairy products. One result of these restrictions is often social isolation for patients with PKU, given the limited selection of natural foods that can be eaten, the important role of food in our social interactions, and the time burden (planning, assessing, calculating, and

recording food intake) required for adherence to MNT. Therefore, for the majority of adults with PKU it is universally recognised that chronic low phenylalanine intake with medical food is not sustainable and is an unacceptable or unreasonable chronic treatment option for adults with PKU. The largest barriers to the successful maintenance of the lifelong phenylalanine restricted dietary regimen are poor palatability, limited selection, limited availability of formulas and medical food, and social isolation.

Despite supplementation of vitamins, stringent MNT has been associated with nutritional deficiencies, such as vitamin B12 and other B vitamins, vitamin D, folate, and calcium. Reliance on nutritionally incomplete medical foods has been shown to increase the risk for obesity, bone pathology, and heart disease (Enns, 2010; Moseley, 2002; Macleod, 2010).

Sapropterin is currently the only pharmacologic treatment option for PKU patients. It is a synthetic form of the PAH co-factor, BH4 and is only effective as an adjunct to MNT in a subpopulation of BH4-responsive PKU patients with residual PAH activity. Therefore, the majority of adult patients are not able to achieve control of their phenylalanine levels with existing therapy.

The important identified risks associated with sapropterin (Kuvan Summary of Product Characteristics [SmPC], 2020) are:

- Vomiting, diarrhoea, abdominal pain (≥1/100 to <1/10).
- Hypophenylalaninaemia (≥1/100 to <1/10). Active management of dietary phenylalanine and overall protein intake while taking Kuvan® is required to ensure adequate control of blood phenylalanine and tyrosine levels and nutritional balance.
- Rebound effect as defined by an increase in blood phenylalanine levels above pre-treatment levels, may occur upon cessation of treatment.
- Drug interactions with dihydrofolate reductase inhibitors, vasodilators using the nitric oxide (NO) metabolic pathway and levodopa.

Nephrotoxicity is an important potential risk for sapropterin.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

If not treated at birth, HPA can lead to rapid mental retardation. Initiation of treatment in infancy has reduced the proportion of patients with irreversible brain damage, low intelligence quotient (IQ), and lowered the high incidence of other neurological and psychiatric co-morbidities.

In patients with PKU, elevated phenylalanine levels in the blood and brain tissues, HPA, are toxic to the central nervous system (CNS) and can result in neurological and

psychiatric pathology, and psychological and neurocognitive dysfunction, if not treated. (Bilder, 2016; Bilder, 2017; NPKUA 2014):

- Neurological pathology: seizures, tremor, migraine, and probably long-term neurodegeneration.
- Psychiatric: depression, anxiety.
- Psychological: mood, inattention, impulsivity, confusion, anger, reduced vitality, tiredness, agoraphobia.
- Neurocognitive: executive function, verbal memory, inhibitory control, working memory, cognitive flexibility.
- Executive function: planning, problem solving, information processing, bringing previous experience to bear on activities, and sustained attention.

The prevalence of psychiatric and neurologic symptoms in adults with early treated PKU is higher than the US National Institutes of Health (NIH) estimates for disease prevalence in adults in the general population (NIMH, 2013). Specifically, 49% of adults with PKU reported inattention symptoms versus 4% of adults in the general population who reported attention deficit hyperactivity disorder (ADHD); 22% of adults with PKU reported anxiety symptoms versus 3% of adults in the general population who reported generalised anxiety disorder; and 18% of adults with PKU reported depression symptoms versus 7% of adults in the general population who reported major depressive disorder (PKU Systematic Review and Meta-Analysis).

HPA and prolonged MNT can also result in nutritional deficits (Enns, 2010), dysfunctional metabolic control and bone pathology (Hoeks, 2009; Camp, 2014; Hvas, 2006; Schulz, 1995; Sarkissian, 2008), and increased diabetic and cardiovascular (CV) risk factors (eg, increased lipids, homocysteine, and body mass index [BMI]) (Moseley, 2002; Macleod, 2010).

The majority of patients in Europe are now screened and effectively treated at birth and so the majority of adults who have avoided significant neurological damage, retained their IQ.

Important co-morbidities:

Co-morbidities of PKU relate to the condition itself and reflect the level of treatment. Other than the conditions discussed above, a review of the literature did not reveal any other comorbidities occurring in this patient population.

In terms of concomitant medication these tend to follow the co-morbidities above such as the prescription of anti-depressants and anxiolytics although these conditions seem more resistant to treatment when associated with HPA.

Other medication follows the management of conditions that are associated with increased age but are probably more common at an earlier age in PKU patients such as

H2 antagonists and proton pump inhibitors (PPI), anti-hypertensive and lipid lowering medication and drugs to control type II diabetes; all driven by a tendency to increased obesity in the PKU population.

Module SII: Non-clinical part of the safety specification

The nonclinical programme includes single- and repeat-dose pharmacodynamic (PD), safety pharmacology, toxicokinetic, and toxicity evaluations in ENU2 mice, rats, and Cynomolgus monkeys. The pharmacological activity of pegvaliase has been demonstrated in a PKU model, the ENU2 mouse. Respiratory and CNS safety pharmacology was evaluated in rats, and CV safety pharmacology was assessed in telemeterised monkeys. The pharmacokinetics (PK) of pegvaliase was evaluated in ENU2 mice and in conjunction with the toxicology and toxicokinetic (TK) studies in rats and monkeys. Single- and repeat-dose toxicity studies were conducted in rats and monkeys. Reproductive toxicity studies, including the evaluation of pegvaliase effects on fertility and embryo-foetal development pre- and post-natal development following daily dosing of pegvaliase have also been conducted in rats and rabbits. Genotoxicity and carcinogenicity studies were not conducted for this programme.

Key Safety Findings	Relevance to Human Usage
Toxicity:	
Single-dose Toxicity The single-dose toxicity and TK of pegvaliase was evaluated when administered as a subcutaneous (SC) injection in rats at 10, 25 or 250 mg/kg (Study 165 07-003). In rats given a single dose at 250 mg/kg, swelling at the injection site 3 to 4 days post-dose and red or scaly skin during the second week post-dose were attributed to the total volume of PEGylated product administered. There was decreased body weight gain in the 250 mg/kg group without a qualitative change in food consumption. There were no changes in organ weights across dose groups and no pegvaliase related macroscopic findings. Kupffer cell vacuolation was observed in the livers of most rats that were treated with 250 mg/kg. The no-observed-adverse-effect-level (NOAEL) of pegvaliase when administered to rats was 250 mg/kg as a single dose SC injection. The single-dose toxicity and TK of pegvaliase were evaluated when pegvaliase was administered as a single SC injection to Cynomolgus monkeys at 4, 12, or 60 mg/kg (Study 165 07-007). There were no clinical signs of toxicity observed over the course of the study in animals treated with 4 or 12 mg/kg pegvaliase. Monkeys given 60 mg/kg pegvaliase exhibited morbidity between 3 and 5 days post dose including some or all of the following: depression, dehydration, anorexia, hypothermia/cold to touch, diarrhoea, hunched posture, hypoactivity, vomitus containing food, and weight loss. These signs led to the early termination of the entire group less than 1 week post-dose due to associated findings secondary to the PD effect of pegvaliase in lowering plasma phenylalanine to non-detectable levels. Clinical laboratory findings at Day 6 or 7 included decreased total serum protein due to decreased albumin concentration. Due to this exaggerated pharmacology of limiting phenylalanine and subsequent decreased protein synthesis, animals became lethargic with reduced food consumption, dehydration, body weight loss, and hypothermia. At necropsy, macroscopic erosions and discolourations were noted throughout the gastrointestinal tract; most animals had single or multifocal pyloric mucosal ulceration and some animals had ileocecal junction or distal colon discolourations. These gastrointestinal lesions, specifically the pyloric mucosal ulcerations observed in the 60 mg/kg group, were most likely due to a secondary stress response induced by the decreased protein synthesis, and thus, were considered pegvaliase-related. There was no dose related histopathologic findings in animals treated with 4 or 12 mg/kg of pegvaliase. The NOAEL of pegvaliase when administered to monkeys as a single SC injection was 12 mg/kg.	

Repeated-dose toxicity The repeat-dose toxicity and TK of pegvaliase was evaluated in rats given 1, 8, or 25 mg/kg pegvaliase SC twice weekly for 28 days with a 2 week recovery period (Study 165 07 009). The NOAEL of pegvaliase when administered SC to rats twice weekly for 4 weeks was 25 mg/kg. The key findings were minimal vacuolation of reticuloendothelial cells of the spleen in a subset of animals.	
The repeat-dose toxicity and TK of pegvaliase was also evaluated in rats given 1, 8, or 25 mg/kg/dose pegvaliase SC twice weekly for 26 weeks with a 12 week recovery period (Study 165-08-019). The NOAEL of pegvaliase when administered SC to rats twice weekly for 26 weeks was 1 mg/kg. The key findings were vacuolation/hypertrophy of renal tubule epithelial cells; vacuolation of histiocytic cells in liver, spleen, testes, adrenal cortex, mesenteric lymph node and mandibular lymph node. Because the vacuolation/hypertrophy of renal tubule cells persisted in the kidney without evidence of reversibility, the toxicologic importance of this finding was considered uncertain.	The vacuolation observed only in the rat toxicology studies was not associated with any functional changes as determined by clinical chemistry/urinalysis. The changes seen in the rat were not seen in Cynomolgus monkeys suggesting that such changes were species specific. In clinical studies whilst there were 43 adverse events (AEs) reported which could be considered potentially indicative of renal impairment, 39 of these were transient and resolved despite ongoing treatment with pegvaliase with no action taken. One event resulted in dose reduction and two in discontinuation. Forty of these 43 events resolved, with 3 events unresolved at the time of the last report. No consistent clinically significant laboratory findings (UACR, serum creatinine and serum cystatin C) indicative of renal toxicity, was observed in patients. Experience with PEG and PEGylated biopharmaceuticals shows that no functional changes related to PEG, for organs and tissues where cellular vacuolation was seen in animal toxicology studies, have been reported with 11 approved drugs (Ivens, 2015). The vacuolation findings in the rat do not constitute an important safety concern.
The repeat-dose toxicity and TK of pegvaliase was evaluated in Cynomolgus monkeys given 0.01, 0.1, and 1 mg/kg SC twice weekly for 28 days with a 4 week recovery phase on a subset of animals (Study 165-07-008). The NOAEL of pegvaliase when administered SC to monkeys twice weekly for 4 weeks was 0.01 mg/kg/dose. The key finding was slight vascular degeneration of medium, muscular arteries in a subset of animals. The repeat-dose toxicity and TK of pegvaliase was also evaluated in Cynomolgus monkeys given 0, 0.01, 0.1, 1, and 3 mg/kg/dose and 7 mg/kg/dose reduced to 5 mg/kg/dose and further reduced to 3 mg/kg/dose SC twice weekly for 39 weeks with a 13-week recovery phase on a subset of animals (Study 165 07-030). The key findings were varying degrees of arterial inflammation of small arteries and arterioles in a wide range of organs in a subset of animals. Based on the findings of arterial inflammation of the small arteries and arterioles after 39 weeks of twice weekly administration of pegvaliase, SC in monkey, the NOAEL was 1 mg/kg.	Arterial inflammation observed in monkeys was attributed to the immune-mediated response associated with chronic administration of an exogenous protein to the animals and was reversible upon cessation of treatment. As the arterial inflammation observed in the monkeys had unknown translatability to humans, robust clinical monitoring is ongoing for any signs or symptoms of potential immune complex mediated disease and includes evaluations for potential kidney injury and vasculitis and for other signs and symptoms of immune complex disease. To date, no evidence of immune complex mediated end-organ damage has been identified in the clinical studies; assessment included

Key Safety Findings	Relevance to Human Usage
	review of AEs and laboratory findings potentially associated with immune complex formation including, but not limited to: proteinuria/albuminuria; hematuria; events suggestive of renal impairment; elevations in blood creatinine; increased liver function tests or events involving hepatic impairment; lymphadenopathy; serositis; hemolysis; Grade≥3 myalgia and Grade≥3 arthralgia/arthritis. In clinical studies, whilst 48 subjects were identified as having adverse events which potentially could be related to cutaneous vasculitis, on review of the narratives none of the cases were clinically assessed by the sponsor to be cutaneous vasculitis. No supporting skin biopsies were performed. Of note, the majority of these events were transient and resolved while on continued treatment. Cutaneous vasculitis is not therefore considered to be an important safety concern. However, complications of Immune-complex formation remain a potential risk for a medication intended for lifelong administration and therefore is considered to be an Important Potential Risk for Pegvaliase in this RMP.
Reproductive/developmental toxicity The effects of pegvaliase on fertility and embryonic/embryofoetal development, was conducted in male and female rats given daily SC administration of 2, 8 or 20 mg/kg pegvaliase before cohabitation and through mating, implantation and closure of the hard palate (Study 165-12-037). Reproductive toxicities in this study in animals treated with pegvaliase at > 8 mg/kg/day included reduced number of implantations compared to control animals. Litter size and foetal weights were also reduced in animals treated with 20 mg/kg/day pegvaliase. The percentage of foetuses per litter with alterations was increased in rats treated with > 8 mg/kg/day pegvaliase. In Study 165-11-027, pregnant female rabbits received SC administration of pegvaliase at 2, 5 or 20 mg/kg. The key findings were weight loss, anorexia and hypoactivity. Increased foetal resorptions, reduced foetal body weights and increased foetal alterations. In a study evaluating embryofoetal development, pregnant female rabbits received SC administration of pegvaliase at 2 or 5 mg/kg/day (Study 165-12-036). There were dose dependent reductions in maternal body weight gain that corresponded to decreased food consumption and increased abortions in rabbits treated with 5 mg/kg/day. There were reduced foetal body weights at≥2 mg/kg/day and increased embryo/foetal lethality and	Pregnancies were reported in 15 female subjects (with 17 pregnancies) and 17 female partners (20 pregnancies) of male subjects during the clinical studies. The outcomes in 8 female pregnancies (7 subjects) were: still birth (with placental abruption), missed abortion (high maternal Phe levels), therapeutic abortion, induced birth due to mild gestational hypertension (neonate reportedly doing well), spontaneous abortion, microcephaly (high maternal Phe levels), respiratory distress syndrome and microcephaly (high maternal Phe levels), and Grade 3 prolonged labour leading to delivery of a normal neonate by Caesarean section. Of the 9 remaining pregnancies (in 8 of 14 subjects who became pregnant), 6 pregnancies were reported to have a normal outcome, 2 resulted in an elective or therapeutic abortion, and 1 resulted in a neonate with a transient mild systolic murmur that resolved without intervention.

Key Safety Findings	Relevance to Human Usage
foetal malformations and variations at 5 mg/kg/day. Based on the results of this study, the NOAEL for maternal and developmental toxicity was less than 2 mg/kg/day at any given dose interval during embryogenesis. In a study evaluating developmental and peri-/post-natal reproduction including postnatal behavioural and functional evaluation, female rats received SC administration of pegvaliase before cohabitation through lactation and weaning (Study 165-14-13) at doses of 2, 8, or 20 mg/kg/day. There were reduced body weight gains and food consumption in females given 20 mg/kg/day pegvaliase with an associated increased number of dams with all pups dying on postpartum days 1 to 4 and pup deaths through postnatal day 7. Doses of 20 mg/kg/day significantly reduced the viability and lactation indices, average litter size, and average pup weights. Reductions in body weight in pups were observed in the 20 mg/kg/day maternal dose group. After weaning, reduced body weights were observed until postnatal day 43, after which body weight and body weight gains were comparable to all other dose groups including the vehicle control group. Maternal doses of pegvaliase as high as 20 mg/kg/day did not affect pups learning and memory, mating and fertility or any parameter evaluated at Caesarean section. Based on the results of this study, the NOAEL for both general and reproductive toxicity was considered to be 8 mg/kg/day. Data in rats have shown excretion of pegvaliase in milk at doses of > 2 mg/kg/day (exposure 4.4 times the maximum recommended human dose, of 40 mg/day).	In the 20 partner pregnancies (involving 17 partners of male subjects), 11 pregnancies had a reported normal outcome. For the other 9 pregnancies, 7 were reported with an unknown outcome, one neonate had respiratory distress and 1 resulted in a spontaneous abortion. Foetal developmental toxicity will be considered an Important Potential Risk. Pegvaliase is excreted in milk in rats but it is not known whether pegvaliase is excreted in human breast milk. Use in breastfeeding women will be considered Missing Information.
Fertility No pegvaliase-related effects were observed on any mating and fertility parameters in males or females at doses as high as 20 mg/kg/day.	The nonclinical findings do not raise any important safety concerns for human use.
Genotoxicity and Carcinogenicity Genotoxicity and carcinogenicity studies were not conducted for this product in accordance with the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use S1A, “Carcinogenicity studies are not generally needed for endogenous substances given essentially as replacement therapy”. ICH S6 (R1) guidelines indicates that “Standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals”.	Not applicable.

Key Safety Findings	Relevance to Human Usage
Safety Pharmacology:	
Cardiovascular system, including potential effect on the QT interval The CV effects of a single SC injection of 0, 1, 3, or 10 mg/kg pegvaliase were evaluated in conscious telemetry instrumented Cynomolgus monkeys (Study 165 07 006). CV effects assessed were electrocardiogram (ECG) and hemodynamic (systolic, diastolic, and mean arterial pressures), inotropic state, heart rate, and abdominal temperature. No direct effects on cardiac rhythm, QT interval, or corrected QT interval (QTc) were observed at doses up to 10 mg/kg pegvaliase. No physiologically important changes were observed in hemodynamic data, inotropic state, heart rate or abdominal temperature.	The nonclinical findings do not raise any important safety concerns for human use.
Central nervous system The CNS effects of a single SC dose of 0, 10, 50, and 125 mg/kg pegvaliase administered to male and female rats were evaluated before dosing and at approximately 6, 24, 48, and 72 hours post dose (Study 165 07-004). Each animal underwent a modified Irwin neurological assessment including a battery of behavioural tests and clinical observations. A reduction in body weight gain was seen in the high dose (125 mg/kg) group compared to control animals by Day 6 after dose administration. No changes in CNS parameters were noted in the pegvaliase treated rats for any portion of the modified Irwin assessment at SC doses up to 125 mg/kg.	The nonclinical findings do not raise any important safety concerns for human use.
Respiratory system The respiratory effects of a single SC injection of 0, 10, 50, and 125 mg/kg pegvaliase were assessed in male rats (Study 165 07-005). Respiratory parameters included tidal volume, respiration rate, and minute volume. A single SC dose of up to 125 mg/kg of pegvaliase administered to male rats caused no alterations in respiratory function parameters evaluated in this study.	The nonclinical findings do not raise any important safety concerns for human use.

Conclusions of non-clinical data

Safety concern	Conclusion
Important Identified Risks	None
Important Potential Risks	Complications of immune complex formation Foetal developmental toxicity
Missing Information	Use in breastfeeding women

Module SIII: Clinical trial exposure

Subject exposure to pegvaliase is supported by data from 7 completed clinical studies in adults with PKU representing a total of 355 subjects with PKU who have been exposed to at least one dose of pegvaliase as of 17 April 2019.

Table SIII.1. Exposure to Pegvaliase in BioMarin Clinical Trials

Study	No. of Subjects Treated	Phase	Study Design	Study Type Study Status
PAL-001	**25**	1	First-in human single dose pegvaliase naive	Safety completed
PAL-002 Subjects who were initially enrolled in PAL-001	**40** 11	2	Dose-finding multiple dose	Safety/efficacy completed
PAL-004	**16**	2	Dose-finding multiple dose pegvaliase naive	Safety/efficacy completed
165-205	**24**	2	Dose-finding multiple dose pegvaliase naive	Safety/efficacy completed
PAL-003 Subjects who were initially enrolled in PAL-002 Subjects who were initially enrolled in PAL-004 Subjects who were initially enrolled in 165-205	**68** 33 15 20	2	Long term extension multiple dose	Safety/efficacy completed
165-301	**261**	3	Multiple dose pegvaliase naive	Safety/efficacy completed
165-302 Subjects who were enrolled into 165-302 from **165-301** Subjects who were enrolled into 165-302 from **165-205** Subjects who were enrolled into 165-302 from **PAL-003** Subjects in 165-302 who started pegvaliase in PAL-002 and enrolled into PAL-003 Subjects in 165-302 who started pegvaliase in PAL-004 and enrolled into PAL-003 Subjects in 165-302 who started pegvaliase in 165-205 and enrolled into PAL-003	**215** 203 1 11 3 5 3	3	Multiple dose 4-part study	Safety/efficacy (Parts 1, 2, 3 4 completed)

The following populations have been defined:

- Safety Population: All subjects who received at least one dose of pegvaliase in any study: 355 subjects.
- Multiple dose (MD) Population: A subset of the safety population comprising of all subjects who received >1 dose of pegvaliase in a Phase 2 or Phase 3 study; ie excludes subjects who received a single dose in PAL-001: 341 subjects.
- Induction/Titration/Maintenance (I/T/M) Population: includes all subjects who were administered pegvaliase using the induction, titration and maintenance regimen which informs the proposed label treatment regimen. This population includes data from subjects first enrolled in the parent studies 165-205 or 165-301 and from the subsequent extension studies to which they transferred PAL-003 and 165-302: 285 subjects

The I/T/M dosing regimen constitutes the data to support the Marketing Authorisation Application. It is the most clinically relevant population because it resulted in the majority of subjects achieving substantial blood phenylalanine reduction (from naïve baseline) and for characterisation of the safety risks the I/T/M Population is the primary focus.

Safety data from MD Population and the single dose phase 1 PAL-001 study are presented only where relevant.

Table SIII.2. Duration of Exposure (to 17 April 2019)

Subjects by duration of treatment, n (%)	I/T/M Population (N=285)	MD Population (N=341)
≥ 6 months	229 (80.4%)	275 (80.6%)
≥ 1 year	209 (73.3%)	254 (74.5%)
≥ 2 years	181 (63.5%)	221 (64.8%)
≥ 3 years	160 (56.1%)	196 (57.5%)
≥ 4 years	84 (29.5%)	117 (34.3%)
≥ 5 years	26 (9.1%)	56 (16.4)
≥ 6 years	4 (1.4%)	33 (9.7%)
Total treatment exposure (person-years) [a]	**789.4**	**1056.7.**

[a] The duration in months was calculated from the first dose to the last dose administered across all studies in which a subject was enrolled. Intervals of missing doses that were > 28 consecutive days were excluded from the calculation of treatment duration.

Table SIII.3. Exposure by Dose Level (I/T/M Population)

Dose Level Range [a]	Number of Subjects	Treatment Exposure (Person-Years) [b]
Placebo [c]	28	4.4
> 0 and < 20 mg/day	285	159.8
≥ 20 and < 40 mg/day	257	180.9
≥ 40 and < 60	223	335.5
≥ 60 mg/day	98	113.0
Total	**285**	**793.6**

[a] Each dose level group included all subjects who received a daily dose of pegvaliase within the specified dose range. Subjects could have been included in more than one dose level group.

[b] Total treatment exposure was aggregated duration of treatment across all subjects (for each subject, time from the first dose to the last dose administered across all studies in which the subject was enrolled). Intervals of missing doses that were >28 consecutive days were excluded from the calculation of treatment duration.

[c] Includes subjects who received placebo during Part 2 of 165-302.

Table SIII.4. Exposure by Gender (I/T/M Population)

Gender	Number of Subjects	Treatment Exposure (Person-Years)[a]
Male	142	420.5
Female	143	373.1
Total	**285**	**793.6**

[a] Time was months from the first dose to the last dose administered across all studies in which a subject was enrolled. Intervals of missing doses that were >28 consecutive days were excluded from the calculation of treatment duration.

Table SIII.5. Exposure by Age Group (I/T/M Population)

Age Group	Number of Subjects	Treatment Exposure (Person-Years)[a]
16 to 18 years	12	35.1
18 to < 65 years	273	758.5
Total	**285**	**793.6**

[a] Time was months from the first dose to the last dose administered across all studies in which a subject was enrolled. Intervals of missing doses that were >28 consecutive days were excluded from the calculation of treatment duration.

Table SIII.6. Exposure by Ethnicity (I/T/M Population)

Ethnicity	Number of Subjects
Hispanic or Latino	7
Not Hispanic or Latino	277
Missing	1
Total	**285**

[a] Time was months from the first dose to the last dose administered across all studies in which a subject was enrolled. Intervals of missing doses that were >28 consecutive days were excluded from the calculation of treatment duration.

Table SIII.7. Exposure by Race (I/T/M Population)

Race	Number of Subjects
Asian	0
Black or African American	3
White	278
Other	3
Missing	1
Total	**285**

Clinical studies with pegvaliase to date have excluded patients who are pregnant or lactating, as well as those with underlying organ pathology such as hepatic, renal, or cardiac impairment. Despite the exclusion criteria, 15 female subjects (17 pregnancies) on pegvaliase treatment became pregnant. No studies have been conducted in renal or hepatically impaired subjects. In order to better identify subjects in the last three categories, BioMarin has reviewed baseline laboratory results and medical histories to attempt to determine if any patients with pre-existing renal, hepatic, or cardiac impairment were enrolled in a pegvaliase study. Exposure in special populations is presented in Table SIII.8:

Table SIII.8. Exposure in Special Populations (All Clinical Studies)

Special Population with PKU	Persons	Person-Years
Pregnant women	15	53.06
Lactating women	0	NA
Paediatric subjects <18 years old	14	43.29[a]
Hepatic impairment		
Subjects in any study with a reported history of hepatic impairment or whose baseline aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels were ≥2x upper limit normal (ULN)	0	NA
Renal impairment		
Subjects in any study with a reported history of renal impairment or whose baseline BUN and/or creatinine levels were ≥ 2x ULN	0	NA
Cardiac impairment	1[b]	3.70

NA, not applicable.

[a]. The total exposure in these 14 subjects also includes exposure during the periods when the subjects were ≥ 18 years.

[b] One subject in Study 165-205 had diastolic dysfunction recorded as medical history at Baseline.

Module SIV: Populations not studied in clinical trials

The important exclusion criteria in the clinical studies are listed below.

SIV.1: Exclusion criteria in pivotal clinical studies within the development programme

Exclusion Criterion	Reason for Exclusion	Is it considered to be included as missing information? If no, rationale.
Known hypersensitivity to active substance or excipient of pegvaliase.	Excluded as a precautionary measure in view of the safety risk.	No. The SmPC Section 4.3 states that severe systemic hypersensitivity reaction or recurrence of a mild to moderate acute systemic hypersensitivity reaction to pegvaliase, or any of the excipients listed in SmPC Section 6.1 is a contraindication for pegvaliase administration. Hypersensitivity reactions have been well characterised as a result of clinical trial experience. 75% of patients experienced hypersensitivity reactions and 6% of patients experienced 25 acute systemic hypersensitivity reactions. Based upon the above, known hypersensitivity to the active substance or excipient of pegvaliase is not missing information. Pegvaliase will be contraindicated in patients who have experienced a severe systemic hypersensitivity reaction or a recurrence of a mild to moderate acute systemic hypersensitivity reaction.
Pregnant, breastfeeding, or considering pregnancy.	Animal reproductive studies in rats and rabbits indicate developmental defects including 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 were associated with the dose-dependent decreases in blood phenylalanine levels to below normal levels achieved with pegvaliase in non-PKU animals. It is not known whether pegvaliase is excreted in human milk. Reproductive data in rats have shown excretion of	No. Although there is limited data from the use of pegvaliase in pregnant women, animal studies have shown maternal reproductive toxicity that was associated with decreased blood phenylalanine concentrations below normal levels. Although this effect may be due to the pharmacodynamics effect of pegvaliase, foetal developmental toxicity is considered to be an Important Potential Risk. In animal studies, pegvaliase was excreted in breast milk but it is not known if this is excreted in human breast milk. Use in breastfeeding women is therefore Missing Information.

Exclusion Criterion	Reason for Exclusion	Is it considered to be included as missing information? If no, rationale.
	pegvaliase in milk at doses of > 2 mg/kg/day (exposure 4.4 times the maximum recommended human dose, of 40 mg/day).	
Subjects <16 years of age (Lower age limit increased from 16 years to 18 years in 2014).	Excluded as a precautionary measure due to potential impact of pegvaliase on long-term intellectual and psycho-social development.	Yes (unpredictable immune-mediated response with off label use in patients < 16 years of age).
Subjects >70 years of age.	Adults older than ~60 years did not benefit from neonatal screening or from dietary restriction therapy. Therefore, these subjects are at greater risk for serious neurological sequelae of HPA and are unlikely to be recruited for clinical trial participation or to meet inclusion/exclusion criteria. Therefore, experience in this subgroup is limited.	Yes (> 65 years) as there were no such patients in the I/T/M Population.
If on medication for ADHD, depression, or other psychiatric disorder, not on a stable dose of medication for ≥ 8 weeks prior to enrolment or willing to maintain stable dose during study.	PKU is often associated with neuropsychiatric complications. A stable dose of these medications would prevent confounding of efficacy variables measured in the Phase 3 studies for improvement in inattention, mood and executive function due to lowering of blood phenylalanine level following treatment with pegvaliase.	No. There is no reason to believe that dose changes in co-administered medications for ADHD, depression, or other psychiatric disorders within the prescribed limits will pose any safety risk.
Use of any medication intended to treat PKU, including the use of large neutral amino acids, within 2 days prior to the administration of pegvaliase.	Large neutral amino acids may cause reduction in phenylalanine levels thus potentially impacting the efficacy and safety endpoints.	No. Treatment options for adults with PKU are limited to sapropterin and disease management with MNT with severe restrictions on dietary protein intake. Palynziq is indicated for the treatment of patients with PKU 16 years or older who have inadequate blood phenylalanine control (blood phenylalanine levels greater than 600 µmol/L). Whilst concomitant use of sapropterin and pegvaliase could potentially cause hypophenylalaninaemia, such an effect is anticipated by the mechanisms of action and this does not constitute missing information.

Exclusion Criterion	Reason for Exclusion	Is it considered to be included as missing information? If no, rationale.
Use or planned use of any other injectable drugs containing PEG, including medroxyprogesterone injection, within 3 months prior to screening and during study participation.	Pegvaliase, just like other PEGylated proteins, has the potential to elicit an immune response, and thus may sensitise patients to other PEGylated injectables.	No. Acute systemic hypersensitivity reactions in patients taking other concurrent injectables containing PEG is considered to be an Important Potential Risk.
ALT >2 times ULN.	Excluded as a precautionary measure.	Yes. Use in patients with pre-existing hepatic impairment.
Creatinine >1.5 times the ULN.	Excluded as a precautionary measure.	Yes. Use in patients with pre-existing renal impairment.
History of organ transplantation or on chronic immunosuppressive therapy.	Excluded as precautionary measure. Similar to other biologics, pegvaliase has the potential for immunogenicity and related adverse events (AEs). Immunosuppressive therapy may mask the emergence of drug-associated safety findings.	No. It is unlikely that sufficient numbers of patients with organ transplantation or on chronic immunosuppressive therapy within this rare disease population are going to seek treatment with pegvaliase.

SIV.2: Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as those that occur uncommonly (≥1/1,000 and < 1/100), those caused by prolonged exposure, those due to cumulative effects or those with a long latency. In the I/T/M group, 285 subjects were exposed to pegvaliase and of these 84 (29.5%) subjects were exposed for ≥ 4 years.

SIV.3: Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.3.1. Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposures
Pregnant women	Pregnant women were excluded from the clinical trials. In the clinical trial population, there were 15 (with 17 pregnancies) pregnancies in female subjects and 19 in female partners of male subjects.
Breastfeeding women	Breastfeeding women were excluded from the clinical development programme.
Patients with relevant comorbidities: • Hepatic impairment • Renal impairment • Immunocompromised	Patients with hepatic impairment, renal impairment, history of organ transplantation and chronic immunosuppressive therapy were excluded from the clinical trials.
Population with relevant different racial or ethnic origin	There was no restriction in the clinical studies on the ethnicity or race of the subjects to be included. Majority of subjects (97.4%) were White, which is expected based on the epidemiology of the disease. There is no reason to suspect a different safety profile in adult PKU patients of different ethnicities.
Paediatric patients	The age criterion was amended in the Phase 3 studies to increase the lower age limit from 16 years old to 18 years old per feedback from the Food and Drug Administration (Food and Drug Administration [FDA] Advice/information request; 14 May 2014). A total of 14 subjects (12 subjects in I/T/M) in the age group of 16 to 18 years, enrolled prior to the amendment, continued in the studies.
Elderly patients	Elderly patients (≥ 70 years of age) were excluded from the clinical development programme. The oldest subject enrolled was 56 years of age.

Module SV: Post-authorisation experience

SV 1 Post-authorisation exposure

SV 1.1: Method used to calculate exposure

Cumulative patient exposure from marketing experience is estimated for patients exposed to Palynziq via commercial, free drug (patients receiving free drug were defined as patients provided with Palynziq but not recorded as receiving at least 1 commercial dose), and named patient uses combined. BioMarin tracks how many patients receive Palynziq therapy and the source of the drug they receive: commercial, free drug, or named patient use. The patient numbers quoted below therefore, are not calculated using a formula based on the number of pre-filled syringes sold. The exact number of patients using the product are pulled out of the BioMarin company tracking system. Patient counts in this RMP are based on the information in the system as of 23 May 2021.

The information on pre-filled syringes sold/distributed comes directly from the sales system, which keeps records of cumulative units sold.

SV 1.2 Exposure

Estimated global marketed exposure is summarized in Table SV.1. Estimated marketed exposure is summarized by region in Table SV.2

Table SV.1: Estimated Global Marketed Exposure Data

PBRER #	PBRER reporting period	Pre-filled Syringes Sold/Distributed (n)	Global Marketed Exposure Data (Patients)			
			Commercial and Named Patient Use[a]	Free Drug[b]	Total # of Patients	Change in Total # of Patients from Prior Period (%)
1	24 November 2018 to 23 May 2019[c]	58,773	521	12	533	NA
2	24 May 2019 to 23 November 2019	108,907	811	14	825	55
3	24 November 2019 to 23 May 2020	154,858	1039	11	1050	225 (27)
4	24 May 2020 to 23 November 2020	193,908	1217	40	1257	207 (20)
5	24 November 2020 to 23 May 2021	232,312	1432	23	1455	198 (16)

NA, not applicable; PBRER, Periodic Benefit Risk Evaluation Report

[a] Syringes sold are specific to the PBRER reporting period.

[b] Patient totals are cumulative from beginning of commercial sales through the current PBRER period. Patients receiving free drug patients were defined as patients provided with Palynziq but not recorded as receiving at least 1 commercial dose.

[c] Includes data from the start of commercial use to 23 May 2021.

Table SV 2: Estimated Marketed Exposure Data by Country

PBRER reporting period	Country	Pre-filled Syringes Sold/ Distributed (n)[a]	Global Marketed Exposure Data (Patients)			
			Commercial and Named Patient Use[b]	Free Drug[b]	Total # of Patients (n)	Change in Total # of Patients from Prior Period (%)
24 November 2018 to 23 May 2019	United States	58,621	521	12	533	NA
	Saudi Arabia	152	0	0	0	NA
24 May 2019 to 23 November 2019	United States	108,199	804	14	818	53
	Saudi Arabia	500	0	0	0	0
	United Kingdom	54	0	0	0	0
	Germany	154	7	0	7	NA
24 November 2019 to 23 May 2020	United States	150,043	1006	11	1017	199 (24)
	Saudi Arabia	500	4	0	4	NA
	United Kingdom	0	0	0	0	NA
	Germany	4,315	29	0	29	22 (314)
24 May 2020 to 23 November 2020	United States	181,822	1171	40	1211	194 (19)
	Saudi Arabia	1204	4	0	4	0
	United Kingdom	0	0	0	0	NA
	Germany	10,263	42	0	42	13 (45)
	Qatar	140	Not Available	0	NA	NA
	Lebanon	427	Not Available	0	NA	NA
	Greece	12	Not Available	0	NA	NA
	Kuwait	40	Not Available	0	NA	NA
24 November 2020 to 23 May 2021	United States	215,075	1364	23	1387	176 (15)
	Saudi Arabia	1,623	6	0	6	2 (50)
	United Kingdom	0	0	0	0	NA
	Germany	14,576	58	0	58	16 (38)
	Qatar	280	Not Available	0	NA	NA
	Lebanon	0	Not Available	0	NA	NA
	Greece	184	Not Available	0	NA	NA
24 November 2020 to 23 May 2021	Kuwait	350	Not Available	0	NA	NA
	Argentina	199	4	0	4	NA
	Spain	23	Not Available	0	NA	NA
	Italy	2	Not Available	0	NA	NA

NA, not applicable; PBRER, Periodic Benefit Risk Evaluation Report

[a] Syringes sold are specific to the PBRER reporting period.

[b] Patient totals are cumulative from beginning of commercial sales through the current PBRER period. Patients receiving free drug patients were defined as patients provided with Palynziq but not recorded as receiving at least 1 commercial dose.

Treatment of patients under 18 years of age is considered as off-label use in the US as per the approved Palynziq United State Prescribing Information (USPI). There has been a total of 45 patients under 18 years of age who have been prescribed Palynziq post authorisation in the US as of 01 June 2021 (closest data cut to 23 May 2021). These include 45, 8, 4 and 1 patient who were 17, 16, 15, and 10 years of age respectively (USA Palynziq Risk Evaluation and Mitigation Strategy [REMS] Program).

One patient 66 years of age, one patient 67 years of age, and 2 patients 68 years of age are receiving doses of Palynziq post authorization according to data from the REMS registration (USA Palynziq REMS Program).

Treatment of patients < 16 years of age is off-label use in the EU. Data regarding the use of Palynziq in this population are not always available as a result of patient privacy laws in the EU.

Review of the limited number of adverse events received from US patients under 18 years of age have not highlighted any unpredictable immune responses in this age group.

Module SVI: Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Pegvaliase has no known potential for misuse for illegal purposes.

Module SVII: Identified and potential risks

SVII.1: Identification of safety concerns in the initial RMP submission

Safety Concerns	
Important identified risks	Acute systemic hypersensitivity reaction Angioedema Serum sickness Hypophenylalaninaemia Persistent arthralgia (≥ 6 months) Severe injection site reactions
Important potential risks	Complications of Immune Complex Formation resulting in end-organ damage Foetal developmental toxicity Unpredictable immune-mediated response with off-label use in patients < 16 years Acute systemic hypersensitivity reactions in patients taking other concurrent injectables containing PEG
Missing information	Long-term safety and tolerability Use in the elderly over 65 years of age Use in patients with pre-existing hepatic impairment Use in patients with pre-existing renal impairment Use in breastfeeding women

SVII.1.1: Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risk	Reason for Risk(s) not being Considered Important
Headache, Cough Nausea Erythema Pruritus Abdominal pain Rash Vomiting Myalgia Joint stiffness Joint swelling Musculoskeletal stiffness Complement C3 (C3) levels decreased Complement C4 (C4) levels decreased High sensitivity c-reactive protein (CRP) levels increased Alopecia Dizziness	Risks with minimal clinical impact on patients (in relation to the severity of the indication treated).
Lymphadenopathy Urticaria Skin exfoliation Maculopapular rash Dyspnoea	Known risks that do not impact the risk-benefit profile.
Medication error	Palynziq is supplied as a pre-filled syringe. Initial administration(s) should be performed under supervision of a healthcare professional. Prior to independent self-administration, the patient should demonstrate competency in self injection. No cases of medication error occurred in clinical studies.

SVII.1.2: Risks considered important for inclusion in the list of safety concerns in the RMP

Risk-benefit impact: Important Identified Risk: Acute systemic hypersensitivity reactions

Whilst the majority of these reactions were mild to moderate, four subjects in the I/T/M Population had 5 episodes which met Brown's criteria for severe episodes of an acute systemic hypersensitivity reaction. While all events resolved without need for intubation or vasopressors, such reactions have the potential to lead to serious outcomes. However, by implementing the risk minimisation measures which are set out in the SmPC and patient information leaflet (PL), and in the Educational Materials for healthcare providers (HCPs) and patients and trained observers including the patient card, the risk is manageable. The safety profile will be derived from routine pharmacovigilance activities and an observational exposure study (165-501). Additionally, following a review by the Pharmacovigilance Risk Assessment Committee (PRAC) of PBRER #3 (EMEA/H/C/PSUSA/00010761/202005) "anaphylaxis" was added to the list of adverse drug reactions with an unknown frequency to reflect the data received from post-marketing sources where it has not been possible to establish the underlying mechanism. The addition of anaphylaxis to the SmPC alerts prescribers to the possibility that acute systemic hypersensitivity reactions consistent with anaphylaxis may have a mechanism distinct from the Type III immune-complex mediated hypersensitivity characterised for these events in the clinical trial program. This addition did not have an impact on the risk minimisation measures outlined in this RMP as they are applicable for the management of an acute systemic hypersensitivity reaction or anaphylaxis, irrespective of the underlying mechanism.

Risk-benefit impact: Important Identified Risk: Angioedema

Angioedema is considered an Important Identified Risk due its potential to be a component of acute hypersensitivity reaction. However, the majority of the reports of angioedema were not associated with an acute hypersensitivity reaction. Given the low rate of occurrence, the mild to moderate presentation of symptoms, and the fact that the majority of subjects remained on treatment without requiring a dose reduction or interruption, there is minimal impact on risk-benefit. However, by implementing the risk minimisation measures which are set out in the SmPC and PL, and in the Educational Materials for HCPs and patients and trained observers including the patient card, the risk is manageable. The safety profile will be derived from routine pharmacovigilance activities, and an observational exposure study (165-501).

Risk-benefit impact: Important Identified Risk: Serum sickness

Seven subjects experienced serum sickness in the I/T/M Population. Three of these 7 episodes were severe and 2 were serious. Two subjects discontinued treatment and 5 subjects continued treatment without experiencing a recurrence; serum sickness in these 5 subjects was managed with drug interruption, dose reduction, and/or concomitant medication.

All events were of short duration (1 to 8 days) and all 7 subjects recovered without sequelae. Taking these factors into account, there is minimal impact on the risk-benefit.

The safety profile will be derived from routine pharmacovigilance activities, and an observational exposure study (165-501).

Risk-benefit impact: Important Identified Risk: Hypophenylalaninaemia

Approximately forty-six (46%) percent of the patients experienced hypophenylalaninaemia. Hypophenylalaninaemia can be managed with routine monitoring of blood phenylalanine levels. The effect of hypophenylalaninaemia is unknown, other than the effect during pregnancy. Proper monitoring is required to minimise the risk and consequences of hypophenylalaninaemia to ensure an acceptable risk-benefit balance. The safety profile will be derived from routine pharmacovigilance activities and an observational exposure study (165-501). In addition, Study 165-503 (US only) will evaluate the effect of immunologic responses on blood phenylalanine. Study 165-504 will evaluate foetal and infant outcomes in women with PKU exposed to pegvaliase during pregnancy and during breastfeeding.

Risk-benefit impact: Important Identified Risk: Persistent arthralgia (≥ 6 months)

Eighty-six (86%) percent of the patients experienced arthralgia. Most of the cases were mild to moderate in severity. Seven (7%) percent of the patients experienced persistent arthralgia (≥ 6 months). The risk of persistent arthralgia may have significant impact on quality of life (QOL).

The safety profile will be derived from routine pharmacovigilance activities, and an observational exposure study (165-501).

Risk-benefit impact: Important Identified Risk: Severe injection site reactions

Ninety-three (93%) percent of the patients experienced injection site reactions of which only one case was severe. The risk of severe injection site reaction may have significant impact on the QOL. The injection site should be checked for redness, swelling, or tenderness.

The safety profile will be derived from routine pharmacovigilance activities, and an observational exposure study (165-501).

Risk-benefit impact: Important Potential Risk: Complications of immune complex formation resulting in end-organ damage

Whilst there is a theoretical risk of end organ damage due to immune complex formation, there have not been any confirmed reports associated with pegvaliase in the I/T/M Population. There is therefore no impact on the risk-benefit. The safety profile will be derived from studies 165-501 and 165-503 (US).

Risk-benefit impact: Important Potential Risk: Foetal developmental toxicity

Animal studies have shown reproductive toxicity associated with decreased maternal blood phenylalanine concentrations below normal levels. Uncontrolled blood phenylalanine levels before and during pregnancy are associated with an increased risk for miscarriage and major birth defects and hence continued and stable control of phenylalanine levels during pregnancy is essential to reduce the incidence of phenylalanine-induced effects on the foetus.

Pregnant and breastfeeding subjects were excluded from the clinical trial population.

The effects of pegvaliase on foetal development will be assessed through routine pharmacovigilance and by a prospective global pregnancy observational safety surveillance study (165-504).

Risk-benefit impact: Important Potential Risk: Unpredictable immune-mediated response with off-label use in patients < 16 years

In the I/T/M Population, 12 subjects between the ages of 16 to 18 years were treated and 14 subjects overall.

The safety profile in patients less than 16 years of age could potentially differ from the adult population. The immaturity of their immune system could result in differences in immune mediated responses. Pegvaliase will be indicated for the treatment of adult patients. However, recognising the limitations of alternative treatment for PKU (MNT with or without sapropterin), it can be anticipated that pegvaliase could be prescribed off label for this patient population.

Off label use in this population will be assessed by routine pharmacovigilance activities and by an observational exposure study (165-501).

Risk-benefit impact: Important Potential Risk: Acute systemic hypersensitivity reactions in patients taking other concurrent injectables containing PEG

Subjects using other injectables containing PEG were excluded from clinical trials. As all PEGylated proteins have the ability to illicit an immune response, there is the potential for the safety profile of pegvaliase to differ in this patient population.

Safety in this patient population will be assessed by routine pharmacovigilance activities and by an observational exposure study (165-501).

Risk-benefit impact: Missing Information: Long term safety and tolerability

Although at the data cut off 84/285 (29.5%) subjects have been dosed for ≥4 years in the I/T/M Population, the risk of circulating immune complexes (CIC) mediated end organ damage remains an Important Potential Risk with a treatment which is intended to be used for the lifetime of the patient. Therefore, further longer-term data are needed to assess impact of chronic low level CICs. The global observational pegvaliase drug exposure study (165-501) is aimed at further characterising the long-term safety of pegvaliase under standard of care practices.

Risk-benefit impact: Missing Information: Use in patients > 65 years

In the I/T/M Population, the oldest subject studied was 56 years of age. The age of the study population reflected the implementation of neonatal screening and as such no subjects over 60 years of age were included in the clinical studies. Safety in patients over the age of 65 years is in need of further characterisation as it can be anticipated that, with time, these patients will be candidates for treatment. Safety in this population will be assessed by routine pharmacovigilance activities and by an observational exposure study (165-501).

Risk-benefit impact: Missing Information: Use in patients with pre-existing hepatic impairment

There were no hepatic concerns raised in the nonclinical studies, however subjects with hepatic impairment, (baseline ALT > 2 times the ULN) were excluded from clinical studies.

Safety in this patient population will be assessed by routine pharmacovigilance activities and by an observational exposure study (165-501).

Risk-benefit impact: Missing Information: Use in patients with pre-existing renal impairment

There were no significant renal concerns raised in the nonclinical studies. However, subjects with renal impairment (as evidenced by serum creatinine > 1.5 times ULN) were excluded from clinical studies as a precautionary measure as the PEG component of pegvaliase is renally cleared.

Safety in this patient population will be assessed by routine pharmacovigilance activities and by an observational exposure study (165-501).

Risk-benefit impact: Missing Information: Use in breastfeeding women

Breastfeeding subjects were excluded from the clinical trial population.

Whilst pegvaliase is excreted in the milk of rats, it is not known whether pegvaliase is excreted in human milk.

The safety in this patient population will be assessed through routine pharmacovigilance and by a prospective global pregnancy observational safety surveillance study (165-504).

SVII.2: New safety concerns and reclassification with a submission of an updated RMP

No new safety concerns were identified up to data lock for this RMP.

SVII.3: Details of important identified and potential risks from clinical development and post-authorisation experience (including newly identified)

Table SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risk: Acute systemic hypersensitivity reactions	
Potential mechanisms	Acute systemic hypersensitivity reactions were most frequent during induction and titration phase (5% of patients; 19 episodes over mean treatment duration of 13 months) and decreased in maintenance phase (2% of patients; 6 episodes over mean treatment duration of 33 months). The risk of an acute systemic hypersensitivity reaction occurring is 6-fold higher in induction/titration phase compared to maintenance phase. The observed increases in CIC levels in conjunction with C3/C4 reduction, suggests that the mechanism of hypersensitivity reactions, including acute systemic hypersensitivity reactions (where drug-specific immunoglobulin E [IgE] testing around the time of the event was negative) was Type III IC-mediated hypersensitivity. In clinical trials, of the sixteen subjects who had acute systemic hypersensitivity reaction episodes, 10/16 (62.5%) subjects were subsequently re-dosed with pegvaliase and 4/10 subjects had recurrences of acute systemic hypersensitivity reactions. The ability to rechallenge subjects, the observed increases in CIC levels in conjunction with C3/C4 consumption and the lack of drug-specific IgE suggests that the mechanism of acute systemic hypersensitivity reaction in the pegvaliase clinical studies was Type III immune complex-mediated hypersensitivity and not IgE-mediated Type I hypersensitivity, which is generally associated with an immediate exaggerated response upon re-exposure to an allergen. Based on PRAC request on the review of PBRER #3, anaphylaxis has also been added to the list of adverse drug reactions in Table 2: Adverse Reactions in patients treated with Palynziq, with an unknown frequency to reflect the data received from post-marketing sources where it has not been possible to establish the underlying mechanism. The addition of anaphylaxis to the SmPC alerts prescribers to the possibility that acute systemic hypersensitivity reactions consistent with anaphylaxis may have a mechanism distinct from the Type III immune-complex mediated hypersensitivity characterised for these events in the clinical trial program. The risk minimisation measures outlined in this RMP are applicable for the management of an acute systemic hypersensitivity reaction or anaphylaxis, irrespective of the underlying mechanism.
Evidence source(s) and strength of evidence	Clinical trial data from the I/T/M Population. Acute systemic hypersensitivity reactions are not unanticipated for an enzyme substitution therapy and the rate of these reactions in the clinical programme and the lack of other aetiological factors (the exception being one episode which developed 22 hr after the most recent dose of pegvaliase confounded by concurrent amoxicillin and fluconazole use) in the 25 episodes which developed in the I/T/M Population provide strong evidence that these episodes are related to pegvaliase treatment.
Characterisation of the risk	All reported AEs that could be potential manifestations of acute systemic hypersensitivity reaction in the pegvaliase safety population were

Important Identified Risk: Acute systemic hypersensitivity reactions	
	identified using the Broad Algorithmic anaphylactic reaction Standardised Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ), a modified Hypersensitivity SMQ, reports of anaphylaxis or anaphylactoid reactions by site physicians, and all events where adrenaline was administered as a treatment intervention. Evaluations were performed first by the Sponsor conservatively applying all three National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network (NIAID/FAAN) clinical diagnostic criteria for potential anaphylaxis episodes (which characterise AEs as anaphylaxis based on presenting signs and symptoms rather than on a particular immune-mediated or non-immunologic mechanism), which were then further evaluated by an independent academic expert allergist/immunologist, whereby each case was assessed using clinical experience and medical judgement to determine whether NIAID/FAAN criteria were met and to assess the clinical significance of reported signs and symptoms. The frameworks described in NIAID/FAAN criteria (Sampson, 2006) and Brown'scriteria (Brown, 2004) were utilised as the basis for assessing severity. All the adjudicated subjects fitted the definition for criteria #1 of Sampson'sCriteria,which,whereas follows: Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING: Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) Reduced BP or associated symptoms of end- organ dysfunction (eg, hypotonia [collapse], syncope, incontinence). Additionally, the adjudicator considered whether signs/symptoms were clinically significant to meet NIAID/FAAN Criteria. Brown'scriteria,wereusedtojudgeifsubjecthadexperiencedaBrown's "severe"reaction.Thisisdefinedas hyperoxia,withaperipheraloxygen saturation (SpO_2) of 92% or lower and systolic hypotension of <90mmHg, as well as signs of severe neurological compromise. All episodes adjudicated as acute systemic hypersensitivity reaction involved dermatologic symptoms of systemic rash, urticaria, pruritus, flushing and/or angioedema with varied respiratory symptoms. The only CV sign noted was hypotension, but this was uncommon. The respiratory symptoms were more subjective with shortness of breath rarely with wheezing.Thefoursubjects,experiencing5episodes whichmetBrown's severe criteria in the I/T/M Population had either cyanosis or a temporary drop in oxygen saturation less than or equal to 92% or a temporary drop in systolic blood pressure or syncope. For example, one subject had a fall in SpO2 to 86% with a normal tryptase, and one subject had a drop in systolic blood pressure to 90 mmHg with syncope for 60-90 seconds. In those episodes adjudicated as not consistent with an acute systemic hypersensitivity reaction, there was an absence of significant associated respiratory or CV signs or symptoms alongside the dermatologic manifestations; and in some instances the external expert did not consider that the dermatologic manifestations reported met NIAID/FAAN criteria. This approach identified 16 (6%) subjects with 25 episodes of acute systemic hypersensitivity reaction in the I/T/M Population with a rate of 0.03 episodes/person-year. Acute systemic hypersensitivity reactions

Important Identified Risk: Acute systemic hypersensitivity reactions	
	generally occurred within 1 hour after injection (88%; 22/25 episodes); however, delayed reactions have occurred (up to 24 hours). The median duration of the acute systemic hypersensitivity reaction episodes was 1 day. Premedication was used for 16/25 episodes. All 16 subjects tested negative for drug specific IgE at or near the time of each acute systemic hypersensitivity reaction. Acute systemic hypersensitivity reactions were most frequent during the Induction and Titration phases (5% of subjects; 19 episodes) and decreased in Maintenance Phase (2% of subjects; 6 episodes). Acute systemic hypersensitivity reactions were managed by administration of adrenaline (epinephrine) (10/16 patients for 11/25 episodes), corticosteroids, antihistamines, and/or oxygen. Four out of the 16 patients (1% of I/T/M Population; 0.01 episodes/person-year) experienced 5 severe episodes of an acute systemic hypersensitivity reaction (as per Brown's criteria, 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], and syncope. Treatment was discontinued in all four patients. Acute systemic hypersensitivity reactions were managed by administration of adrenaline (10/16 patients; 11/25 episodes including all severe episodes meeting Brown's criteria), corticosteroids, antihistamines, and/or oxygen under emergency medical care. Ten out of the 16 patients who experienced acute systemic hypersensitivity reactions were rechallenged and 4 patients had at least one recurrence. Seven out of the 16 patients discontinued treatment. All acute systemic hypersensitivity reaction episodes resolved without sequelae.
Risk groups or risk factors	Baseline antibody positivity was not associated with higher rates of hypersensitivity reactions or acute systemic hypersensitivity reactions. Immune response to pegvaliase does not predict acute systemic hypersensitivity reactions. There was no dose relationship.
Preventability	There were no predictive factors identified to anticipate the occurrence of acute systemic hypersensitivity reactions in particular patients. Risk mitigation strategies implemented in May 2014 in the Phase 3 clinical programme led to reduction of risk of severe acute systemic hypersensitivity reactions from 0.04 episodes/person-year (before implementation of the strategies) to 0.00 episodes/person-year (after implementation of these strategies). 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 (if applicable) 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.

Important Identified Risk: Acute systemic hypersensitivity reactions	
	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 µmol/L while on a stable dose). Patients should 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. For at least the first 6 months of treatment, an observer must be present during and for at least 60 minutes after each administration. An observer is someone who can be present with the patient during and for at least 60 minutes after Palynziq administration, is able to recognise the signs and symptoms of an acute systemic hypersensitivity reaction, call for emergency medical support and administer adrenaline, if warranted. After 6 months of Palynziq treatment, the need for an observer may be reconsidered. 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. 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 done with premedication under the supervision of a healthcare professional with the ability to manage acute systemic hypersensitivity reactions. Prescribing physician should continue or consider initiating or resuming use of premedication. Advice above will be set out in the SmPC and PL. Educational materials for healthcare professionals and patients and trained observers including the patient card (in Part V.2) will reinforce this advice.
Impact on the risk-benefit balance of the product	The risk minimisation strategies for acute systemic hypersensitivity reactions appeared to be successful in reducing the rate of severe reactions (as per Brown's severe hypersensitivity criteria) in the clinical trials and will be part of risk management. By implementing risk minimisation measures, the benefit risk balance is positive. Routine and additional pharmacovigilance activities will further characterise this risk with respect to number of reports, seriousness, outcome, and risk factors and whether experience in the post marketing setting is consistent with the information already known for this risk from clinical trial data.
Public health impact	By implementing the risk minimisation measures described above, it is expected that the overall outcome of these events on a population level will be favourable and hence there is not expected to be any significant public health impact.
Important Identified Risk: Angioedema	
Potential mechanisms	As per acute systemic hypersensitivity reaction above, the mechanism is considered to be Type III IC-mediated hypersensitivity.
Evidence source(s) and strength of evidence	Clinical trial data from the I/T/M Population. As for acute systemic hypersensitivity reactions, the development of angioedema is not unanticipated for an enzyme substitution therapy, and the rate of these reactions, the underlying type III mechanism and lack of other aetiological factors provide evidence that these episodes are most likely related to pegvaliase treatment.

Important Identified Risk: Angioedema	
Characterisation of the risk	A total of 21 (7.4%) subjects experienced 37 episodes of angioedema in the I/T/M Population with a rate of 0.05 episodes/person-year. The following methodology was used and is considered to reflect the likely incidence of angioedema manifestations. **Step 1** –Identified all reported AEs suggestive of angioedema using the Angioedema HLT search which includes the following 21 PTs: angioedema, circumoral oedema, eyelid oedema, face oedema, Gleich's syndrome, hereditary angioedema, idiopathic angioedema, intestinal angioedema, laryngeal oedema, laryngotracheal oedema, lip oedema, lip swelling, mouth swelling, oculorespiratory syndrome, oedema mouth, oropharyngeal swelling, periorbital oedema, pharyngeal oedema, swelling face, swollen tongue and tongue oedema. **Step 2** - BioMarin then clinically assessed the retrieved data identified from Step 1 to assign concurrent events into episodes and to exclude: False positive cases that have clear complicating factors which impact assessment, e.g. onset of event(s) ≥ 30 days after last dose or events/ episodes with a very clear alternative aetiology, i.e. throat swelling secondary to intubation. Cases were **not** excluded, e.g. where the events had long duration which may be atypical for angioedema, or where events occurred concurrent with other conditions which **may** have contributed to their development (e.g. eye swelling reported during episode(s) of seasonal allergy). Episodes which occurred as part of an acute systemic hypersensitivity reaction and which therefore are already included in the incidence for acute systemic hypersensitivity reactions (to avoid duplication). Within 37 episodes of angioedema, 43 AE preferred terms (PTs) were reported. All reported PTs were Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 (31 episodes in 16 [5.6%] subjects) or Grade 2 (6 episodes in 5 [1.8%] subjects) and there were no Grade 3 or 4 angioedema AEs. The 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) occurred independent of acute systemic hypersensitivity reactions. Angioedema was most frequent during the Induction and Titration Phases (5.6% of subjects; 27 episodes over mean treatment duration of 13 months) and decreased in Maintenance Phase (2.8% of subjects; 10 episodes over mean treatment duration of 33 months). The risk of angioedema occurring is 4.5-fold higher in induction/titration phase compared to maintenance phase. There was no relationship between dose and incidence of angioedema. The mean (standard deviation [SD]) time to onset of the angioedema episode from the most recent pegvaliase dose was 26.8 (114.90) hr with a median (range) time to onset of <0.1 (<1 [i.e. immediately following dosing] to 696) hours. Of the 9/37 angioedema episodes where time to onset was evaluable, 5 episodes occurred within 24 hours of injection, 3 episodes occurred between 24 hours and up to 4 days and one subject experienced an episode (reported AE of swollen tongue, that lasted for a day, for which the dosing was interrupted) 29 days (696 hours) after last dose received. The mean (SD) time from the first pegvaliase exposure to occurrence of the first angioedema episode was 228.1 (294.10) days with a median (range) of 91 (4 to 1222) days.

Important Identified Risk: Angioedema	
	The mean (SD) and median (range) duration of an angioedema episode was 4.2 (11.3) days and 1.0 (1 to 64) days, respectively. Premedication was used for 25/37 (67.6%) episodes. 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 37 episodes of angioedema resolved without sequelae. Angioedema can also present as one of the symptoms of an acute systemic hypersensitivity reaction.
Risk groups or risk factors	There were no specific groups identified as having a higher risk of developing angioedema.
Preventability	There were no predictive factors identified to anticipate the occurrence of angioedema in particular patients. Angioedema can also present as one of the symptoms of an acute hypersensitivity reaction. 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 (if applicable) 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. 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 µmol/L while on a stable dose). Patients should 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. For at least the first 6 months of treatment, an observer must be present during and for at least 60 minutes after each administration. An observer is someone who can be present with the patient during and for at least 60 minutes after Palynziq administration, is able to recognise the signs and symptoms of an acute systemic hypersensitivity reaction, call for emergency medical support and administer adrenaline, if warranted. After 6 months of Palynziq treatment, the need for an observer may be reconsidered. 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. 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 initiating or resuming use of premedication.

Important Identified Risk: Angioedema	
	These requirements will be set out in the SmPC and PL. Additionally, educational materials for healthcare professionals and patients and trained observers including the patient card (in Part V.2) will reinforce these requirements.

Important Identified Risk: Angioedema	
Impact on the risk-benefit balance of the product	Given the mild to moderate presentation of symptoms and the fact that the majority of subjects remained on treatment with the majority not requiring a dose reduction or interruption there is minimal adverse impact on the risk-benefit balance of pegvaliase. Routine and additional pharmacovigilance activities will further characterise this risk with respect to number of reports, seriousness, outcome, and risk factors and whether experience in the post marketing setting is consistent with the information already known for this risk from clinical trial data.
Public health impact	The overall outcome of the events of angioedema is that the patient recovers. This, coupled with the fact that the events tend to be mild, suggest that there is minimal public health impact.

Important Identified Risk: Serum sickness	
Potential mechanisms	As serum sickness manifestation is usually as a result of CIC, it is very likely that this is the mechanism in the causation of serum sickness reactions in the pegvaliase studies. Of the seven reported serum sickness AEs six events occurred during the time when CIC formation was at its peak.
Evidence source(s) and strength of evidence	Clinical trial data from the I/T/M Population. There were seven serum sickness AEs reported in the clinical trials and given the immune impact of pegvaliase resulting in CICs, this is likely to be the cause.
Characterisation of the risk	In the I/T/M Population, using the search strategy (which focused on the actual reported PTs of serum sickness or serum sickness-like reaction), 7 AEs in 7 subjects with reported PTs of serum sickness were identified (2%). Serum sickness was most frequent during Induction and Titration Phase (2% of subjects; 6 episodes over mean treatment duration of 13 months) and decreased in Maintenance Phase (0.6% of patients; 1 episode over mean treatment duration of 33 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 treatment (median: 13 days from 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 (median 4 days). Three of these patients experienced severe serum sickness (3/285; 1%), which resulted in treatment discontinuation (2 patients; these 2 events were also reported as serious) or treatment interruption (1 patient). Five of the 7 patients who developed 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.
Risk groups or risk factors	There were no specific groups identified as having a higher risk of developing serum sickness.

Important Identified Risk: Serum sickness	
Preventability	There were no predictive factors identified to anticipate the occurrence of serum sickness in particular patients. The absolute numbers of patients experiencing serum sickness in clinical studies were very small so it is not possible to say definitively whether premedication had an attenuating effect but it is plausible that it did so, given the reduction in numbers and severity of acute hypersensitivity reactions overall post premedication implementation. A description of the events of serum sickness seen from clinical trials is provided in Section 4.8 of the SmPC.
Impact on the risk-benefit balance of the product	Given the low rate of occurrence there is no significant adverse impact on the risk-benefit balance of pegvaliase. Routine and additional pharmacovigilance activities will further characterise this risk with respect to number of reports, seriousness, outcome, and risk factors and whether experience in the post marketing setting is consistent with the information already known for this risk from clinical trial data.
Public health impact	The overall outcome of the events is that the patient recovers. The impact on public health is considered to be minimal.

Important Identified Risk: Hypophenylalaninaemia	
Potential mechanisms	Pegvaliase substitutes for the deficient PAH enzyme activity and reduces blood phenylalanine levels in the body.
Evidence source(s) and strength of evidence	**Non-clinical trials**: Single-dose toxicity studies showed that monkeys given 60 mg/kg pegvaliase exhibited morbidity between 3 and 5 days post dose due lowering plasma phenylalanine to non-detectable levels. **Clinical trials**: Approximately 44% of the patients experienced hypophenylalaninaemia.
Characterisation of the risk	In the I/T/M population, 130 (46%) subjects met the definition of HypoPhe (2 consecutive Phe measurements ≤30 µmol/l), with 266 HypoPhe events, and 155 subjects did not meet the definition (ie, NoHypoPhe). The baseline characteristics were similar between the two subgroups. The majority of subjects (100/125; 80%) who developed HypoPhe had at least one blood Phe measurement of 0 µmol/L during a HypoPhe period. The median time to onset from the first dose of pegvaliase to the first HypoPhe event was 395 days (range 51 to 1546 days) and the median duration of the HypoPhe events was 162 days (range 15 to 1548 days). The duration of the HypoPhe events were similar whether the event occurred in the Titration or the Maintenance Phase. The incidence of early discontinuation of study drug due to AEs was higher in NoHypoPhe subjects (40/155 [25.8%]), than in HypoPhe subjects (2/130 [1.5%]). In the I/T/M population, subject incidences for most AEs were higher in the NoHypoPhe group compared with the HypoPhe group including the overall AEs (100 % vs 96.0%), investigator assessed treatment related AEs (100% vs 82.3%), SAEs (23.2% vs 7.7%) and CTCAE ≥ Grade 3 events (28.4% vs 7.7%). Similarly, the exposure-adjusted rates were higher in the NoHypoPhe group compared with the HypoPhe group for overall AEs (25.80 vs 20.10 events per person-year), investigator assessed treatment related AEs (17.65 vs 8.27 events per person-year), SAEs (0.16 vs 0.09 events per

Important Identified Risk: Hypophenylalaninaemia	
	person-year), CTCAE ≥ Grade 3 events (0.21 vs 0.12 events per person-year). Amongst the AESIs subjects in the NoHypoPhe group had a higher incidence of acute systemic hypersensitivity reactions (9.4% vs 0.8%), HAEs (93.5% vs 71.5%), ISRs (92.3% vs 47.7%), and arthralgia (73.1% vs 31.2%). Exposure-adjusted event rates for AESIs showed a similar general trend, higher in the NoHypoPhe subjects, but the rate was similar for HAEs (6.34 vs 5.74 events per person-year).
Risk groups or risk factors	Unknown.
Preventability	Monitoring of blood phenylalanine level is recommended once a month. During titration and maintenance of Palynziq treatment, patients may develop blood phenylalanine levels below 30 µmol/L. To manage hypophenylalaninaemia, dietary protein intake should be increased to appropriate levels, and then, if needed, the dose of Palynziq should be reduced. Dose reductions are expected to be most effective in managing hypophenylalaninaemia. Patients should be monitored every 2 weeks until blood phenylalanine levels are within a clinically acceptable range. If hypophenylalaninaemia develops prior to reaching daily dosing, the Palynziq 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. Based on animal studies, hypophenylalaninaemia in pregnant women with PKU treated with Palynziq may be associated with adverse foetal outcomes. Blood phenylalanine levels should be monitored more frequently prior to and during pregnancy. Advice will be set out in the SmPC and PL as routine risk minimisation.
Impact on the risk-benefit balance of the product	Uncontrolled blood phenylalanine levels 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. Continued and stable control of phenylalanine levels during pregnancy is essential to reduce the incidence of phenylalanine induced effects on the foetus. Palynziq should not be used during pregnancy unless the clinical condition of the woman requires treatment with pegvaliase. Advice on how to minimise the risk of hypophenylalaninaemia will be disseminated through routine risk minimisation measures to ensure that the benefit-risk for the product remains positive. Routine and additional pharmacovigilance activities will further characterise the risk of hypophenylalaninaemia with respect to number of reports, seriousness, outcome, and risk factors and whether experience in the post marketing setting is consistent with the information already known for this risk from clinical trial data.
Public health impact	The impact on public health is considered to be minimal.

Important Identified Risk: Persistent arthralgia (≥ 6 months)	
Potential mechanisms	Hypersensitivity reactions can manifest as a range of symptoms including arthralgia that could be the result of Type III immune complex-mediated mechanism; tissue deposition of drug-antibody complexes that result in complement activation and inflammation (Galbiati, 2016).
Evidence source(s) and strength of evidence	**Clinical trials**: 86% of the patients experienced episodes consistent with arthralgia (including AEs of, back pain, musculoskeletal pain, pain in extremity, and neck pain). Most of the cases were mild to moderate in severity. Persistent arthralgia (lasting at least 6 months) occurred in 21 (7%) of patients with a total of 28 episodes in the I/T/M Population.
Characterisation of the risk	Of the 285 subjects in the I/T/M Population, 245 (86 %) reported 1,942 AEs of arthralgia (2.45 events per patient-year). Arthralgia occurred as early as the first dose and also occurred at any time during treatment. Arthralgia was most frequent during Induction and Titration phases (79% of subjects; 1269 episodes over a mean treatment period of 13 months likely due to the levels of circulating immune complexes (CIC) being highest during this period and decreased in the Maintenance Phase (67% of patients; 673 episodes over a mean treatment period of 33 months). The median duration of arthralgia was 3 days and 77% of arthralgia episodes had a duration of less than 14 days. Arthralgia persisted up to 936 days (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 (20 episodes). 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. While the specific location on the body for AEs of arthralgia was not systematically collected, a review of the reported verbatim terms for these events shows that the arthralgia events were widespread but more common in the extremities and back. Persistent arthralgia (lasting at least 6 months) occurred in 21 (7%) patients with a total of 28 episodes. Persistent arthralgia occurred as early as 6 days and up to 1,526 days into treatment (median: 554 days from treatment initiation). The dose was not changed for 27 (96%) episodes and dose was reduced for 1 (4%) episode. All persistent arthralgia episodes resolved without sequelae.
Risk groups or risk factors	Female gender.
Preventability	The occurrence of arthralgia is mentioned in section 4.8 of the SmPC.
Impact on the risk-benefit balance of the product	Persistent arthralgia may have a significant impact on the patient QOL. Advice on how to minimise the risk of persistent arthralgia will be disseminated through routine risk minimisation measures to ensure that the benefit-risk for the product remains positive. Routine and additional pharmacovigilance activities will further characterise the risk of persistent arthralgia with respect to number of reports, seriousness, outcome, and risk factors and whether experience in the post marketing setting is consistent with the information already known for this risk from clinical trial data.
Public health impact	The impact on public health is considered to be minimal.

Important Identified Risk: Severe injection site reactions	
Potential mechanisms	An injection site reaction is caused by local allergic reaction or damage to the tissue surrounding where a drug was injected.
Evidence source(s) and strength of evidence	**Clinical trials**: 93% of the patients experienced injection site reactions.
Characterisation of the risk	In the I/T/M Population, 266 (93%) subjects experienced 5,134 AEs related to episodes of ISRs. The majority of ISRs were Grade 1 (62.5%) or Grade 2 (30.5%) in severity, with a single Grade 3 event (0.4%). The most common ISRs (occurring in at least 10% of subjects) were injection site reaction, erythema, bruising, pruritus, pain, swelling, rash, induration and urticaria. ISRs were most frequent during Induction and Titration Phase (90% of patients; 3908 episodes over mean treatment duration of 13 months) and decreased in Maintenance Phase (66% of patients; 1226 over a mean treatment period of 33 months). Injection site reactions occurred as early as the first dose and can occur at any time during treatment. The median duration of injection site reaction was 2 days, and 91% of injection site reactions resolved within 14 days and 99% of injection site reactions resolved by the time of the data cut-off. Three ISRs 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 initiation of treatment and lasted 21 months), and necrobiosis lipoidica diabeticorum (occurred 12 months after initiation of treatment and lasted 12 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.
Risk groups or risk factors	Unknown.
Preventability	The occurrence of severe injection site reactions will be discussed in the SmPC and PL.
Impact on the risk-benefit balance of the product	Severe injection site reactions may have an impact on the patient QOL. Advice on how to minimise the risk of severe injection site reactions will be disseminated through routine risk minimisation measures to ensure that the benefit-risk for the product remains positive. Routine and additional pharmacovigilance activities will further characterise the risk of severe injection site reactions with respect to number of reports, seriousness, outcome, and risk factors and whether experience in the post marketing setting is consistent with the information already known for this risk from clinical trial data.
Public health impact	The impact on public health is considered to be minimal.

Important Potential Risk: Complications of immune complex formation resulting in end organ damage	
Potential mechanisms	IgG and IgM CIC levels were highest during early pegvaliase treatment. The peak in CIC levels during early treatment was associated with a decline in C3 and C4 levels. With continued pegvaliase treatment, CIC and C3/C4 levels trended back toward baseline over time and did not increase after dose increases in long-term treatment. The peak and decline in CIC levels observed during pegvaliase treatment was also associated with a corresponding peak and decline in anti-PEG (IgM and IgG) antibody titre responses. These data suggest that anti-PEG immune complexes (ICs) make up the majority of the total CICs in early treatment. Lower CIC levels later in treatment suggest anti-PAL antibodies are less efficient at forming CICs likely due to the masking of PAL-epitopes by extensive PEGylation. HAEs occurred most frequently during the first 6 months of treatment when anti-PEG responses were peaking, CIC levels were at their highest and C3/C4 levels were at their lowest. The frequency of HAEs declined over time as the immune response matured to a predominantly PAL IgG response, anti-PEG responses diminished to baseline, and CIC and C3/C4 levels trended toward baseline. The temporal association of CIC levels and complement activation with HAEs is consistent with a Type III IC-mediated mechanism of hypersensitivity. An extensive review of the clinical safety data was conducted to evaluate for signs and symptoms associated with IC deposition. No Aes were reported or identified suggesting pegvaliase-associated IC-mediated end organ damage.
Evidence source(s) and strength of evidence	**Clinical trials:** data from the I/T/M Population.
Characterisation of the risk	While mild to moderate Type III HAEs such as fever, arthralgia, rash, non-specific laboratory findings without persistent elevation, and reduced complement levels have occurred with pegvaliase administration, there have been no reports suggestive of pegvaliase associated immune complex mediated end organ damage. There have been no reports of renal failure, haemolytic anaemia, CNS manifestations (such as cerebrovascular accidents or transient ischemic attacks), myocardial ischemic events or confirmed vasculitis suggestive of ongoing immune complex-mediated end-organ damage. There was one report of Immunoglobulin A (IgA) nephropathy in a subject with a long medical history of abnormal renal function which was assessed, both internally and by external renal experts, as a pre-existing condition; and two events of serositis: one was a non-serious Grade 2 AE of pleurisy which developed immediately following an AE of upper respiratory tract infection and the other event was a transient pericardial effusion which was reported as likely having a viral aetiology.
Risk groups or risk factors	No specific preventative measures are in place at this time.
Preventability	While Type III HAEs and laboratory findings such as reduced complement levels have occurred with pegvaliase administration, there have been no reports suggestive of ongoing immune complex-mediated end-organ damage. A major impact on the individual patient is not foreseen at this time.
Impact on the risk-benefit balance of the product	With the current evidence, there is no impact on public health. The risk will be further characterised by routine and additional pharmacovigilance activities.

Important Potential Risk: Complications of immune complex formation resulting in end organ damage	
Public health impact	The impact on public health is considered to be minimal.

Important Potential Risk: Foetal developmental toxicity	
Potential mechanisms	Reduced levels of essential amino acids are critical for synthesis of proteins during foetal development.
Evidence source(s) and strength of evidence	**Non-clinical studies**: Animal studies have shown toxicity associated with decreased maternal blood phenylalanine concentrations below normal levels. Uncontrolled blood phenylalanine levels before and during pregnancy were associated with an increased risk for miscarriage and major birth defects. **Clinical trials**: Pregnant and breastfeeding subjects were excluded from the clinical trial population however despite instructions to avoid pregnancy a few pregnancies occurred and 8 of them were associated with SAEs. Uncontrolled blood phenylalanine levels (hyperphenylalaninemia) 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 intra uterine foetal growth retardation. Additional risk to the unborn child due to hypophenylalaninaemia is not established.
Characterisation of the risk	Despite screening criteria, and instructions to avoid pregnancy, 15 female subjects (with 17 pregnancies) and 17 female partners (20 pregnancies) of male study subjects became pregnant during treatment The outcomes in 8 female pregnancies (7 subjects) were: still birth (with placental abruption), missed abortion (high maternal Phe levels), therapeutic abortion, induced birth due to mild gestational hypertension (neonate reportedly doing well), spontaneous abortion, microcephaly (high maternal high Phe levels), respiratory distress syndrome and microcephaly (high maternal Phe levels), Grade 3 prolonged labour leading to delivery of a normal neonate by Caesarean section. Of the 9 remaining pregnancies (in 8 of 15 subjects who became pregnant), 6 pregnancies were reported to have a normal outcome, 2 resulted in an elective or therapeutic abortion, and 1 resulted in a neonate with a transient mild systolic murmur that resolved without intervention. The 20 outcomes in 17 female partners of male study subjects were: 11 had a normal outcome, no outcome available for 7, one outcome was associated with neonatal respiratory distress (infant required respiratory and nutritional support and was discharged 2 days later) and 1 resulted in a spontaneous abortion.
Risk groups or risk factors	Not applicable.
Preventability	Maternal blood phenylalanine levels must be strictly controlled between 120 and 360 µmol/L both before and during pregnancy. Palynziq is not recommended during pregnancy, unless the clinical condition of the women requires treatment with pegvaliase and alternative strategies to control phenylalanine levels have been exhausted. Advice will be set out in the SmPC and PL as routine risk minimisation.

Important Potential Risk: Foetal developmental toxicity	
Impact on the risk-benefit balance of the product	Uncontrolled blood phenylalanine levels before and during pregnancy may have devastating effects to the foetus. Advice on how to minimise the risk of foetal development toxicity will be disseminated through routine risk minimisation measures to ensure that the benefit-risk for the product remains positive. Routine and additional pharmacovigilance activities will further characterise the risk of foetal development toxicity with respect to number of reports, seriousness, outcome, and risk factors and whether experience in the post marketing setting is consistent with the information already known for this risk from clinical trial data.
Public health impact	The impact on public health is considered to be minimal.

Important Potential Risk: Unpredictable immune-mediated response with off-label use in patients < 16 years	
Potential mechanisms	The innate and adaptive immune systems gradually mature over time. As the individual gets older, he or she develops an expanding repertoire comprising memory T and B cells triggered by previous infections and vaccinations, but also a naive-memory repertoire shaped by exposure to the microbiome, food antigens and inhaled antigens (Simon 2015).
Evidence source(s) and strength of evidence	The pathogenesis and pathophysiology of PKU, driven by an absence or deficiency in PAH enzyme leading to high phenylalanine concentration, is the same in both children and adults. Disease classifications are also similarly categorised across all age groups. The pegvaliase mechanism of action to correct the underlying metabolic deficiency of phenylalanine hydroxylase (PAH) gene is the same in both adults and adolescents (including 16 to <18 year olds). Although the impact of elevated blood phenylalanine and reduced tyrosine may be greater in younger paediatric patients (infants and young children) due to the developing body systems; significant developmental changes in gastrointestinal, central nervous, pulmonary, immune, cardiac and renal systems begin to plateau by 6 years of age to levels seen in adults (FDA Guidance for Industry, Nonclinical Safety Evaluation of Pediatric Drug Products, February 2016). Off-label use in very young children (< 12 years of age) are not anticipated and it is very unlikely that pegvaliase will be used in children 6 years or younger where ongoing development changes in the immune system may result in unpredictable immune mediated responses.
Characterisation of the risk	Not applicable.
Risk groups or risk factors	Female gender.
Preventability	None proposed.
Impact on the risk-benefit balance of the product	Routine and additional pharmacovigilance activities will further characterise the risk of unpredictable immune-mediated response with off-label use in patients < 16 years with respect to number of reports, seriousness, outcome, and risk factors and whether experience in the post marketing setting is consistent with the information already known for this risk from clinical trial data.
Public health impact	The impact on public health is considered to be minimal.

Important Potential Risk: Acute systemic hypersensitivity reactions in patients taking other concurrent injectables containing PEG	
Potential mechanisms	Verhoef and colleagues proposed that immune-mediated side-effects of PEGylated products is based on the haptogenic properties of PEG, responsible for complement activation and the induction of anti-PEG antibodies (Verhoef 2014). 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.
Evidence source(s) and strength of evidence	**Clinical trials**: In the clinical trials, two patients on long term use of a PEGylated medroxyprogesterone acetate product experienced hypersensitivity reactions following single doses of Palynziq.
Characterisation of the risk	There were 2 subjects in the PAL-001 single dose study, excluded from the MD and I/T/M Populations, who were concurrently using another PEGylated injectable, medroxyprogesterone (Depo-Provera), at the time of their pegvaliase dose. These 2 subjects experienced a total of 3 episodes of hypersensitivity reactions (one subject experienced 1 episode and one subject experienced 2 episodes), associated with the use of medroxyprogesterone, of which 1 episode in 1 subject was an acute systemic hypersensitivity reaction meeting the NIAID/FAAN criteria.
Risk groups or risk factors	Unknown.
Preventability	Advice will be set out in the SmPC and PL as routine risk minimisation.
Impact on the risk-benefit balance of the product	Advice on how to minimise the risk will be disseminated through routine risk minimisation measures to ensure that the benefit-risk for the product remains positive. Routine and additional pharmacovigilance activities will further characterise the risk of acute systemic hypersensitivity reactions in patients taking other concurrent injectables containing PEG with respect to number of reports, seriousness, outcome, and risk factors and whether experience in the post marketing setting is consistent with the information already known for this risk from clinical trial data.
Public health impact	The impact on public health is considered to be minimal.

Table SVII.3.2. Presentation of Missing Information

Missing information: Long-term safety and tolerability	
Evidence source	In the clinical trial population, 30.0% of subjects were exposed for ≥ 4 years. Treatment with pegvaliase is intended to be a lifelong treatment and hence it is important to ascertain whether the safety profile remains the same with long-term use. Based on the clinical data, the incidence of Type III hypersensitivity reactions was reduced over time. The occurrence of complications due to immune complex formation has not been seen to date in clinical trials but it is unknown whether or not this will occur with long-term use.
Anticipated risk/consequence of the missing information	Current data have not suggested that any new risks are likely to occur with long-term use. However, it is essential that this is confirmed taking into account the fact that pegvaliase is intended for lifelong use. Long-term safety and tolerability will be assessed through routine pharmacovigilance activities and by an observational drug exposure study (165-501) to evaluate long-term safety of pegvaliase in adults with PKU.

Missing information: Use in patients > 65 years	
Evidence source	In the clinical trial population, the oldest patient studied was 56 years of age. The age of the study population reflected the onset of the implementation of the neonatal screening first introduced in 1961 in US, and as such few subjects who underwent neonatal screening have reached the age of > 65 years.
Population in need of further characterisation	Safety in patients over the age of 65 years will require further characterisation. Over time, the age of the patients eligible for treatment with pegvaliase will increase and as such patients > 65 years of age will be candidates for treatment. Safety in this patient population will be assessed by routine pharmacovigilance activities and by an observational drug exposure study (165-501).

Missing information: Use in patients with pre-existing hepatic impairment	
Evidence source	Subjects with hepatic impairment were excluded from clinical trials
Population in need of further characterisation	Safety in this patient population will be assessed by routine pharmacovigilance activities and by an observational drug exposure study (165-501).

Missing information: Use in patients with pre-existing renal impairment	
Evidence source	Subjects with renal impairment were excluded from clinical trials.
Population in need of further characterisation	Safety in this patient population will be assessed by routine pharmacovigilance activities and by an observational drug exposure study (165-501).

Missing information: Use in breastfeeding women	
Evidence source	Pegvaliase is excreted in the milk of rats but it is not known whether pegvaliase is excreted in human milk.
Population in need of further characterisation	The safety in this patient population will be assessed through routine pharmacovigilance and in study 165-504.

Module SVIII: Summary of the safety concerns

Summary of safety concerns	
Important identified risks	Acute systemic hypersensitivity reaction Angioedema Serum sickness Hypophenylalaninaemia Persistent arthralgia (≥ 6 months) Severe injection site reactions
Important potential risks	Complications of immune complex formation resulting in end-organ damage Foetal developmental toxicity Unpredictable immune-mediated response with off-label use in patients < 16 years Acute systemic hypersensitivity reactions in patients taking other concurrent injectables containing PEG
Missing information	Long term safety and tolerability Use in elderly (> 65 years) Use in patients with pre-existing renal impairment Use in patients with pre-existing hepatic impairment Use in breastfeeding women

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION STUDIES)

III.1: Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaire for reports associated with acute systemic hypersensitivity reaction and serum sickness

The questionnaire will be used to collect structured information on reported suspected adverse reactions.

A copy of this form is provided in Annex 4.

Specific adverse reaction follow-up questionnaire for reports associated with renal adverse events

The questionnaire will be used to collect structured information on reported suspected adverse reactions.

A copy of this form is provided in Annex 4.

The preclinical, clinical laboratory and AE findings in the pegvaliase development program demonstrated that no subjects exhibited a marked change in renal function or developed progressive persistent proteinuria. Therefore, no substantive evidence suggestive of overt renal toxicity was observed in the pegvaliase program. Renal adverse events are not considered an Important Safety Concern in this RMP. Renal function will continue to be carefully monitored in the pegvaliase development program and via routine pharmacovigilance activities post-marketing. A targeted AE follow-up questionnaire for post-marketing reports of renal adverse events will be included. In addition, this topic will be discussed in future PSURs.

A copy of this form is provided in Annex 4.

Other forms of routine pharmacovigilance activities for acute systemic hypersensitivity reactions, serum sickness, angioedema, and renal adverse events:

None

III.2: Additional pharmacovigilance activities

Study short name and title	Rationale and objectives	Study design	Study Population	Milestones
165-501 A multi-center, observational study to evaluate the long-term safety of subcutaneous injections of Palynziq® (pegvaliase) in subjects with phenylketonuria Ongoing	**Primary objective:** • To quantify and characterize the risk of ASHRs/ anaphylaxis, angioedema, serum sickness, severe hypersensitivity reaction, persistent arthralgia (≥ 6 months), severe injection site reaction, hypophenylalaninemia (defined as a blood Phe level ≤ 30 µmol/L for a minimum of 2 consecutive values) in incident-users receiving Palynziq for the treatment of PKU in a real-world setting. **Secondary Objectives:** To quantify and characterize the risk of: • Complications of immune-complex formation or PEG accumulation resulting in end-organ damage, SAEs, severe ADRs, and ADRs leading to treatment interruption or discontinuation and/or study discontinuation in subjects receiving pegvaliase for the treatment of PKU in a real-world setting • Safety events as defined in the primary and secondary objectives in subjects receiving concomitant treatment with other pegylated (PEG) injectables during pegvaliase treatment; subjects ≥ 65 years of age during pegvaliase treatment; subjects with documented pre-existing hepatic impairment during pegvaliase treatment; subjects with documented pre-existing renal impairment during pegvaliase treatment; subjects < 16 years of age receiving pegvaliase treatment excluding Germany; and subjects with hypophenylalaninemia during pegvaliase treatment **Tertiary Objective (EU only):**	Prospective, global observational pegvaliase exposure study	Adult PKU patients	Protocol Submission: 31/Mar/2020 FPI: 31/May/2022 Interim CSR dates: 21/Dec/2021 21/Dec/2023 21/Dec/2025 21/Dec/2027 21/Dec/2029 21/Dec/2031 LPO: 31/May/2032 Anticipated Date of Final CSR: 31/May/2033

Study short name and title	Rationale and objectives	Study design	Study Population	Milestones
	• To evaluate the provision of aRMM to the healthcare provider (HCP) and subject			
165-503 An immunogenicity and inflammation lab study (US only) Planned	**Primary objective:** • To evaluate immunologic and inflammatory responses (immunologic testing, inflammatory markers) associated with incidence of acute systemic hypersensitivity reactions (ASHR)/anaphylaxis, angioedema, serum sickness, and severe immune-mediated adverse drug reactions (ADRs) (ie, generalized skin reactions, injection site reactions, arthralgia, and hypersensitivity) **Secondary Objectives:** • To evaluate immunologic and inflammatory responses (immunologic testing, inflammatory markers) and their effects on major-organ function (eg, kidney function) • To evaluate effect of immunologic responses on blood Phe levels	Immunogenicity/ Inflammation Lab Study	Adult PKU patients (US subset of those enrolled in 165-501)	Protocol Submission: 31/Mar/2020 FPI: 31/Dec/2022 Interim CSR dates: 21/Dec/2021 21/Dec/2023 21/Dec/2025 21/Dec/2027 21/Dec/2029 21/Dec/2031 LPO: 31/Dec/2032 Anticipated Date of Final CSR: 31/Dec/2033
165-504 A Global, Multicenter Study to Assess Maternal, Fetal and Infant Outcomes of Exposure to Palynziq® (pegvaliase) During	**Primary objective:** • To estimate the frequency of pregnancy outcomes (eg, spontaneous abortion, fetal death/stillbirth, live birth, and termination) among subjects with PKU treated with Palyniq during pregnancy and fetal/infant outcomes (all major congenital malformations [MCMs] and specifically microcephaly and congenital heart defects), FGR, small for gestational age [SGA], low birth weight, preterm birth, failure to thrive, and developmental delays) among their offspring exposed to Palynziq during pregnancy.	Prospective global pregnancy observational safety surveillance study	Any consenting female with PKU receiving pegvaliase at any time during pregnancy	Protocol Submission: 31/Mar/2020 FPI: 30/Sep/2022 Interim CSR dates: 21/Dec/2021 21/Dec/2023 21/Dec/2025

Study short name and title	Rationale and objectives	Study design	Study Population	Milestones
Pregnancy and Breastfeeding Ongoing	**Secondary Objectives:** • To compare the frequency of pregnancy outcomes (eg, spontaneous abortion, stillbirth, live birth, and termination) and fetal/infant outcomes (all MCMs and specifically microcephaly and congenital heart defects, FGR, SGA, low birth weight, preterm birth, failure to thrive, and developmental delays) among subjects with PKU treated with Palynziq during pregnancy and their offspring to information on those same outcomes in non-Palynziq exposed, pregnant women with PKU as described in reference literature • To examine differences in the frequency of pregnancy outcomes (eg, spontaneous abortion, stillbirth, live birth, and termination) and fetal/infant outcomes (all MCMs and specifically microcephaly and congenital heart defects, FGR, SGA, low birth weight, preterm birth, failure to thrive, and developmental delays) among subjects with PKU treated with Palynziq during pregnancy and their offspring by maternal blood Phe levels • To estimate the frequency of serious adverse events (SAEs in infants) other than CMs in infants exposed to Palynziq during pregnancy through their first year of life • To estimate the frequency of selected outcomes in subjects with PKU treated with Palynziq during breastfeeding (low milk supply) and their infants (failure to thrive and SAEs) through their first year of life			21/Dec/2027 21/Dec/2029 21/Dec/2031 LPO: 30/Sep/2032 Anticipated Date of Final CSR: 30/Sep/2033
Immune tolerance induction (ITI) regimen study Planned	• To evaluate the ability of the ITI regimen (given prior to or concurrently with pegvaliase) to suppress immune responses, to reduce the risks of immune-mediated adverse reactions, and to enable improved therapeutic responses in adult patients with PKU treated with pegvaliase.	Immune mediated adverse reactions	Adult PKU patients	Protocol Submission: Following completion of FDA feedback

III.3: Summary Table of Additional Pharmacovigilance Activities

Table III.3. On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due Dates
Category 1 – Safety studies imposed as condition of the marketing authorisation.				
Not applicable				
Category 2 – Safety studies which are specific obligations in the context of a marketing authorisation under exceptional circumstances or conditional marketing authorisation.				
Not applicable				
Category 3 – Safety Studies which are required by competent authority				
165-501 A prospective, global observational exposure study. Ongoing	**Primary Objective**: • To quantify and characterize the risk of ASHRs/ anaphylaxis, angioedema, serum sickness, severe hypersensitivity reaction, persistent arthralgia (≥ 6 months), severe injection site reaction, hypophenylalaninemia (defined as a blood Phe level ≤ 30 µmol/L for a minimum of 2 consecutive values) in incident-users receiving Palynziq for the treatment of PKU in a real-world setting **Secondary Objectives**: To quantify and characterize the risk of: • Complications of immune-complex formation or PEG accumulation resulting in end-organ damage, SAEs, severe ADRs, and ADRs leading to treatment interruption or discontinuation and/or study discontinuation in subjects receiving pegvaliase for the treatment of PKU in a real-world setting	• All important Identified and Potential risks will be assessed in this registry. • Use in population not studied in the clinical trials: subjects receiving concomitant treatment with other pegylated (PEG) injectables during pegvaliase treatment; elderly > 65 years, subjects with hepatic impairment, renal impairment and/or hypophenylalaninemia. • The effectiveness of the risk minimisation activities for acute systemic hypersensitivity will also be measured.	Interim CSR dates: Anticipated Date of Final CSR:	21/Dec/2021 21/Dec/2023 21/Dec/2025 21/Dec/2027 21/Dec/2029 21/Dec/2031 31/May/2033

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due Dates
	• Safety events as defined in the primary and secondary objectives in subjects receiving concomitant treatment with other pegylated (PEG) injectables during pegvaliase treatment; subjects ≥ 65 years of age during pegvaliase treatment; subjects with documented pre-existing hepatic impairment during pegvaliase treatment; subjects with documented pre-existing renal impairment during pegvaliase treatment; subjects < 16 years of age receiving pegvaliase treatment excluding Germany; and subjects with hypophenylalaninemia during pegvaliase treatment **Tertiary objective (EU only):** • To evaluate the provision of aRMM to the healthcare provider (HCP) and subject			
165-503 An immunogenicity/ inflammation lab study (US) Planned	**Primary Objective**: • To evaluate immunologic and inflammatory responses (immunologic testing, inflammatory markers) associated with incidence of acute systemic hypersensitivity reactions (ASHR)/anaphylaxis, angioedema, serum sickness, and severe immune-mediated adverse drug reactions (ADRs) (ie, generalized skin reactions, injection site reactions, arthralgia, and hypersensitivity) **Secondary Objectives**: • To evaluate immunologic and inflammatory responses (immunologic testing, inflammatory markers) and their effects on major-organ function (eg, kidney function) • To evaluate effect of immunologic responses on blood Phe levels	• Complications of immune complex formation resulting in end organ damage. • Hypophenylalaninaemia.	Interim CSR dates: Anticipated Date of Final CSR:	21/Dec/2021 21/Dec/2023 21/Dec/2025 21/Dec/2027 21/Dec/2029 21/Dec/2031 31/Dec/2033

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due Dates
165-504 A Global, Multicenter Study to Assess Maternal, Fetal and Infant Outcomes of Exposure to Palynziq® (pegvaliase) During Pregnancy and Breastfeeding Ongoing	**Primary objective** • To estimate the frequency of pregnancy outcomes (eg, spontaneous abortion, fetal death/stillbirth, live birth, and termination) among subjects with PKU treated with Palynziq during pregnancy and fetal/infant outcomes (all MCMs and specifically microcephaly and congenital heart defects], FGR, SGA, low birth weight, preterm birth, failure to thrive, and developmental delays) among their offspring exposed to Palynziq during pregnancy. **Secondary Objective:** • To compare the frequency of pregnancy outcomes (eg, spontaneous abortion, stillbirth, live birth, and termination) and fetal/infant outcomes (all MCMs and specifically microcephaly and congenital heart defects), FGR, SGA, low birth weight, preterm birth, failure to thrive, and developmental delays) among subjects with PKU treated with Palynziq during pregnancy and their offspring to information on those same outcomes in non-Palynziq exposed, pregnant women with PKU as described in reference literature • To examine differences in the frequency of pregnancy outcomes (eg, spontaneous abortion, stillbirth, live birth, and termination) and fetal/infant outcomes (all MCMs and specifically microcephaly and congenital heart defects, FGR, SGA, low birth weight, preterm birth, failure to thrive, and developmental delays) among subjects with PKU treated with Palynziq during pregnancy and their offspring by maternal blood Phe levels	• Foetal developmental toxicity. • Use in breastfeeding.	Interim CSR dates: Anticipated Date of Final CSR:	21/Dec/2021 21/Dec/2023 21/Dec/2025 21/Dec/2027 21/Dec/2029 21/Dec/2031 30/Sep/2033

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due Dates
	• To estimate the frequency of serious adverse events (SAEs) other than CMs in infants exposed to Palynziq during pregnancy through their first year of life • To estimate the frequency of selected outcomes in subjects with PKU treated with Palynziq during breastfeeding (low milk supply) and their infants (failure to thrive and SAEs in infants) through their first year of life.			
Immune tolerance induction (ITI) regimen study Planned	• To evaluate the ability of the ITI regimen (given prior to or concurrently with pegvaliase) to suppress immune responses, to reduce the risks of immune-mediated adverse reactions, and to enable improved therapeutic responses in adult patients with PKU treated with pegvaliase.	Immune mediated adverse reactions.	Protocol submission	Pending conclusion of FDA feedback

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

PART V: RISK MINIMISATION MEASURES

Risk Minimisation Plan

V.1: Routine Risk Minimisation Measures

Table V.1.1. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Acute systemic hypersensitivity reactions (Important identified risk)	Routine risk communication: SmPC Sections 4.2, 4.3, 4.4, 4.7, 4.8. PL Sections 2, 3, 4, 7. Routine risk minimisation activities recommending specific clinical measures to address the risk: For HCPs: Section 4.2 of the SmPC (Method of Administration): 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 µmol/L while on a stable dose). Patients should be instructed to pre-medicate with an H1-receptor antagonist, H2-receptor antagonist, and antipyretic. During maintenance, premedication may be reconsidered for subsequent injections based on patient tolerability to Palynziq. Initial administration(s) should be performed under supervision of a healthcare professional and patients should be closely observed for at least 60 minutes following of each of these initial injections. Prior to first dose of Palynziq, the patient should be trained on the signs and symptoms of an acute systemic hypersensitivity reaction and to seek immediate medical care if a reaction occurs, and how to properly administer adrenaline injection device (auto-injector or pre-filled syringe/pen). Patients should be instructed to carry an adrenaline injection device with them at all times during Palynziq treatment. Prior to independent self-injection, a healthcare professional should train the patient and their observer and assess patient competency on proper self-administration of this medicinal product. 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, 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). Section 4.3 of the SmPC:

Safety Concern	Routine Risk Minimisation Activities
	Contraindication in patients who have had a severe systemic hypersensitivity reaction or recurrence of a mild to moderate acute systematic hypersensitivity reaction. Section 4.4 of the SmPC: Acute systemic hypersensitivity reactions require treatment with adrenaline and immediate medical care. An adrenaline injection device (auto injector or pre-filled syringe/pen) should be prescribed to patients receiving this medicinal product. Patients should be instructed to carry an adrenaline injection device with them at all times during Palynziq treatment. Patients and the trained 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. Patients should pre medicate with an H1 receptor antagonist, H2 receptor antagonist, and an antipyretic. During maintenance, premedication may be reconsidered 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. 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. The prescribing physician should reconsider 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. <u>For patients:</u> Section 2 of the PL: **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). Talk to your doctor, pharmacist, or nurse before using Palynziq. <u>Allergic reactions</u> 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 may give 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. **Stop injecting Palynziq if any of the following symptoms occur:** • Swelling of the face, eyes, lips, mouth, throat, tongue, hands and/or feet

Safety Concern	Routine Risk Minimisation Activities
	• 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 you had a severe allergic reaction. Your doctor will tell you if you can continue Palynziq treatment. <u>Injection of other medicines that contain PEG while using Palynziq</u> 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. Section 3 of the PL: <u>Starting Palynziq</u> 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. <u>Continuing Palynziq</u> • Your doctor will tell you how long to continue taking medicines such as paracetamol, fexofenadine, or ranitidine before you take Palynziq. • For at least the first 6 months of Palynziq treatment, you must have someone with you when you inject Palynziq, and for at least 1 hour

Safety Concern	Routine Risk Minimisation Activities
	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. Section 4 of the PL: - guidance on identifying signs and symptoms of severe systemic hypersensitivity events, including anaphylaxis. Section 7 of the PL: - instructions for administration. <u>Other routine risk minimisation measures beyond the Product Information:</u> Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU.
Angioedema (Important identified risk)	<u>Routine risk communication:</u> SmPC Section: 4.4, 4.8. PL Sections: 2, 4. <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> Section 2 of PL: Advice to stop injecting Palynziq if there is swelling of face, eyes, lips, mouth, tongue, hands and/or feet. <u>Other routine risk minimisation measures beyond the Product Information:</u> Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU.
Serum sickness (Important identified risk)	<u>Routine risk communication:</u> SmPC Section: 4.4, 4.8. PL: Section 4. <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> Section 4 of PL: Advice to contact doctor immediately if a certain type of allergic reaction called serum sickness occurs which includes a combination of fever (high temperature), rash, muscle and joint aches. <u>Other routine risk minimisation measures beyond the Product Information:</u> Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU.
Hypophenylalaninaemia (Important identified risk)	<u>Routine risk communication:</u> SmPC Section: 4.2, 4.4, 4.6. PL: Section 2. <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> Section 4.2 of the SmPC: During titration and maintenance of Palynziq treatment, patients may develop blood phenylalanine levels below 30 µmol/L. To manage

Safety Concern	Routine Risk Minimisation Activities
	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. Patients should be monitored every 2 weeks until blood phenylalanine levels are within a clinically acceptable range. If hypophenylalaninaemia develops prior to reaching daily dosing, the Palynziq 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. Section 4.4 of the SmPC: Monitoring of blood phenylalanine level is recommended once a month. If a patient has a confirmed phenylalanine level below 30 µmol/L, dietary protein intake should be increased to appropriate levels, and then, if needed, the dose of Palynziq should be reduced. In patients experiencing hypophenylalaninaemia despite appropriate levels of protein intake, dose reductions are expected to be most effective in managing hypophenylalaninaemia. Patients who develop hypophenylalaninaemia should be monitored every 2 weeks until blood phenylalanine level is within a clinically acceptable range. The long-term clinical consequences of chronic hypophenylalaninaemia are unknown. Based on animal studies, hypophenylalaninaemia in pregnant women with PKU treated with Palynziq may be associated with adverse foetal outcomes. Blood phenylalanine levels should be monitored more frequently prior to and during pregnancy. Section 4.6 of the SmPC: Maternal blood phenylalanine levels must be strictly controlled between 120 and 360 µmol/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. Section 2 of PL: 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. <u>Other routine risk minimisation measures beyond the Product Information:</u> Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU.
Persistent arthralgia (≥ 6 months) (Important identified risk)	<u>Routine risk communication:</u> SmPC Section: 4.8. PL: Section 4.

Safety Concern	Routine Risk Minimisation Activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU.
Severe injection site reactions (Important identified risk)	Routine risk communication: SmPC Section: 4.2, 4.8. PL: Section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.2 of the SmPC: The injection site should be checked for redness, swelling, or tenderness. Other routine risk minimisation measures beyond the Product Information: Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU.
Complications of immune complex formation resulting in end organ damage (Important potential risk)	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU.
Foetal developmental toxicity (Important potential risk)	Routine risk communication: SmPC Section: 4.4, 4.6. PL: Section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.4 of the SmPC: Blood phenylalanine levels should be monitored more frequently prior to and during pregnancy. Section 4.6 of the SmPC: Maternal blood phenylalanine levels must be strictly controlled between 120 and 360 µmol/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. Other routine risk minimisation measures beyond the Product Information: Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU.
Unpredictable immune-mediated response with off-label use in patients < 16 years (Important potential risk)	Routine risk communication: SmPC Section: 4.2. PL: Section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk:

Safety Concern	Routine Risk Minimisation Activities
	None. Other routine risk minimisation measures beyond the Product Information: Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU.
Acute systemic hypersensitivity reactions in patients taking other concurrent injectables containing PEG (Important potential risk)	Routine risk communication: SmPC Section: 4.4. PL: Section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 2 of the PL. Injection of other medicines that contains PEG while taking Palynziq: Palynziq includes an ingredient called polyethylene glycol (PEG). If you take 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. Other routine risk minimisation measures beyond the Product Information: Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU.
Long term safety and tolerability (Missing information)	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU.
Use in elderly > 65 years (Missing information)	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU.
Use in patients with pre-existing hepatic impairment (Missing information)	Routine risk communication: SmPC Section 5.2. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU.

Safety Concern	Routine Risk Minimisation Activities
Use in patients with pre-existing renal impairment (Missing information)	Routine risk communication: SmPC Section 5.2. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU.
Use in breastfeeding women (Missing information)	Routine risk communication: SmPC Section 4.6. PL Section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Legal Status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU.

V.2: Additional Risk Minimisation Measures

The following risk minimisation activities specifically address the important identified risk of: acute systemic hypersensitivity reactions but are also applicable to angioedema.

Additional Risk Minimisation 1

Physician educational material: Guide for healthcare professionals

Objectives:

Education of HCPs for prevention/management of acute systemic hypersensitivity reactions.

Rationale for the additional risk minimisation activity:

This additional risk minimisation activity is aimed at educating the HCPs for appropriate measures to be considered in order to reduce the incidence and severity of acute systemic hypersensitivity reactions.

Target audience and planned distribution path:

HCPs who are involved in the administration of Palynziq. Educational packs are distributed to the centres, which are responsible for making them available to the HCPs. Educational materials for HCPs will be disseminated prior to launch and if updated will be re-disseminated to all HCPs.

Plans to evaluate the effectiveness of the interventions and criteria for success:

As a process indicator, BioMarin tracks the date of local Health Authority approval in the Member States and date of Educational pack dissemination to the HCPs. Dissemination of Educational packs should occur prior to or at launch, or as agreed by the local Health Authority. The effectiveness of the risk minimisation activities for acute systemic hypersensitivity reaction will be assessed as an outcome measure in Study 165-501 (EU sites only), e.g., collecting confirmation that the treating physician received the guide and the date the treating physician received the guide. The effectiveness is corelated to measure compliance against local approval. Dissemination will occur only after local approval.

Additional Risk Minimisation 2

Patient and trained observer guide

Objectives:

Education of patients, carers, and trained observers for prevention/management of acute systemic hypersensitivity reactions.

Rationale for the additional risk minimisation activity:

This additional risk minimisation activity is aimed at educating the patients and trained observers to recognise signs of acute systemic hypersensitivity reactions so appropriate treatment can be initiated promptly, thus reducing the impact of the event.

Target audience and planned distribution path:

Patients and trained observers who are involved in the administration of Palynziq.

Plans to evaluate the effectiveness of the interventions and criteria for success:

As a process indicator, BioMarin tracks the date of local Health Authority approval in the Member States and date of Educational pack dissemination to the HCPs. Dissemination of Educational packs should occur prior to or at launch, or as agreed by the local Health Authority. The effectiveness of the risk minimisation activities for acute systemic hypersensitivity reaction will be assessed as an outcome measure in Study 165-501 (EU sites only), e.g., collecting confirmation that the treating physician received the guide and the date the treating physician received the guide. The effectiveness is corelated to measure compliance against local approval. Dissemination will occur only after local approval.

Additional Risk Minimisation 3

Patient card

Objectives:

Education of patients for prevention/management of acute systemic hypersensitivity reactions.

Rationale for the additional risk minimisation activity:

This additional risk minimisation activity is aimed at educating patients to recognise signs of acute systemic hypersensitivity reactions so appropriate treatment can be initiated promptly, thus reducing the impact of the event.

Target audience and planned distribution path:

Patients who are involved in the administration of Palynziq.

Plans to evaluate the effectiveness of the interventions and criteria for success:

As a process indicator, BioMarin tracks the date of local Health Authority approval in the Member States and date of Educational pack dissemination to the HCPs. Dissemination

of Educational packs should occur prior to or at launch, or as agreed by the local Health Authority. The effectiveness of the risk minimisation activities for acute systemic hypersensitivity reaction will be assessed as an outcome measure in Study 165-501 (EU sites only), e.g., collecting confirmation that the treating physician received the guide and the date the treating physician received the guide. The effectiveness is corelated to measure compliance against local approval. Dissemination will occur only after local approval.

Removal of Additional Risk Minimisation Activities:

Not applicable.

V.3: Summary of Risk Minimisation Measures

Table V3.2. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation measures	Pharmacovigilance Activities
Acute systemic hypersensitivity reactions (Important Identified Risk)	Routine risk minimisation measures: SmPC Sections 4.2, 4.3, 4.4, 4.7, 4.8. PL Sections 2, 3, 4, 7. Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU. Additional risk minimisation measures: Educational materials for HCPs. Educational materials for Patients and Trained Observers. Patient card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Acute systemic hypersensitivity and serum sickness follow-up form for these adverse reactions. Additional pharmacovigilance activities: Observational pegvaliase exposure study (165-501).
Angioedema (Important Identified Risk)	Routine risk minimisation measures: SmPC Section: 4.4, 4.8. PL Section: 2, 4. Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU. Additional risk minimisation measures: As angioedema may be a symptom of acute systemic hypersensitivity reactions, the same additional risk minimisation measures will apply. Educational materials for HCPs. Educational materials for Patients and Trained Observers. Patient card.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Acute systemic hypersensitivity and serum sickness follow-up form for these adverse reactions. Additional pharmacovigilance activities Observational pegvaliase exposure study (165-501).
Serum sickness (Important Identified Risk)	Routine risk minimisation measures: SmPC Section: 4.4, 4.8. PL: Section 4. Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Acute systemic hypersensitivity and serum sickness follow-up form for these adverse reactions. Additional pharmacovigilance activities

Safety Concern	Risk minimisation measures	Pharmacovigilance Activities
	Additional risk minimisation measures: None.	Observational pegvaliase exposure study (165-501).
Hypophenylalaninaemia (Important Identified Risk)	Routine risk communication: SmPC Section: 4.2, 4.4, 4.6. PL: Section 2. Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Observational pegvaliase exposure study (165-501).
Persistent arthralgia (≥ 6 months) (Important Identified Risk)	Routine risk communication: SmPC Section: 4.8. PL: Section 4. Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Observational pegvaliase exposure study (165-501).
Severe injection site reactions (Important Identified Risk)	Routine risk communication: SmPC Section: 4.2, 4.8. PL: Section 4. Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Observational pegvaliase exposure study (165-501).
Complications of immune complex formation leading to end organ damage (Important Potential Risk)	Routine risk minimisation measures: None. Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Renal adverse event follow-up form for these adverse reactions. Additional pharmacovigilance activities:

Safety Concern	Risk minimisation measures	Pharmacovigilance Activities
	Additional risk minimisation measures: None.	Studies 165-501 and 165-503.
Foetal developmental toxicity (Important Potential Risk)	Routine risk communication: SmPC Section: 4.4, 4.6. PL: Section 2. Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Observational pregnancy pegvaliase exposure study (165-504).
Unpredictable immune-mediated response with off-label use in patients < 16 years (Important Potential Risk)	Routine risk communication: SmPC Section: 4.2. PL: Section 2. Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Observational pegvaliase exposure study (165-501).
Acute systemic hypersensitivity reactions in patients taking other concurrent injectables containing PEG (Important Potential Risk)	Routine risk communication: SmPC Section: 4.4. PL: Section 2. Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Observational pegvaliase exposure study (165-501).
Long term safety and tolerability (Missing Information)	Routine risk minimisation measures: None. Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU. Additional risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Observational pegvaliase exposure study (165-501).

Safety Concern	Risk minimisation measures	Pharmacovigilance Activities
	None.	
Use in elderly > 65 years (Missing Information)	Routine risk minimisation measures: None Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Observational pegvaliase exposure study (165-501).
Use in patients with pre-existing hepatic impairment (Missing Information)	Routine risk minimisation measures: SmPC Section 5.2. Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Observational pegvaliase exposure study (165-501).
Use in patients with pre-existing renal impairment (Missing Information)	Routine risk minimisation measures: SmPC Section 5.2. Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Observational pegvaliase exposure study (165-501).
Use in breastfeeding women (Missing Information)	Routine risk minimisation measures: SmPC Section 4.6. PL Section: 2. Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Observational pregnancy pegvaliase exposure study (165-504).

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

Summary of Risk Management Plan for Palynziq (pegvaliase)

This is a summary of the risk management plan (RMP) for Palynziq. The RMP details important risks of Palynziq, how these risks can be minimised, and how more information will be obtained about Palynziq's risks and uncertainties (missing information).

Palynziq's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Palynziq should be used.

This summary of the RMP for Palynziq should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Palynziq's RMP.

I. The medicine and what it is used for

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 µmol/L) despite prior management with available treatment options. It contains pegvaliase as the active substance and it is given by SC injection.

Further information about the evaluation of Palynziq's benefits can be found in Palynziq's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/palynziq

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Palynziq together with measures to minimise such risks and the proposed studies for learning more about Palynziq's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so as to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Palynziq these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Palynziq is not yet available, it is listed under 'missing information' below.

II.A. List of important risks and missing information

Important risks of Palynziq are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Palynziq. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Acute systemic hypersensitivity reactions • Angioedema • Serum sickness • Hypophenylalaninaemia • Persistent arthralgia (≥ 6 months) • Severe injection site reactions
Important potential risks	• Complications of Immune Complex Formation resulting in end organ damage • Foetal developmental toxicity • Unpredictable immune-mediated response with off-label use in patients < 16 years • Acute systemic hypersensitivity reactions in patients taking other concurrent injectables containing PEG

List of important risks and missing information	
Missing information	• Long term safety and tolerability • Use in elderly > 65 years • Use in patients with pre-existing renal impairment • Use in patients with pre-existing hepatic impairment • Use in breastfeeding women

II.B. Summary of important risks

Important Identified Risk #1: Acute systemic hypersensitivity reactions	
Evidence for linking the risk to the medicine	Clinical trial data from the I/T/M Population. Acute systemic hypersensitivity reactions are not unanticipated for an enzyme substitution therapy and the rate of these reactions in the clinical programme and the lack of other aetiological factors (the exception being one episode which developed 22 hr after the most recent dose of pegvaliase confounded by concurrent amoxicillin and fluconazole use) in the 25 episodes which developed in the I/T/M Population provide strong evidence that these episodes are related to pegvaliase treatment.
Risk factors and risk groups	Baseline antibody positivity was not associated with higher rates of hypersensitivity reactions or acute systemic hypersensitivity reactions. Immune response to pegvaliase does not predict acute systemic hypersensitivity reactions There was no dose relationship.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2, 4.3, 4.4, 4.7, 4.8. PL Sections 2, 3, 4, 7. Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU. Additional risk minimisation measures: Educational materials for HCPs. Educational materials for Patients and Trained Observers Patient card.
Additional pharmacovigilance activities	Observational pegvaliase exposure study (165-501).

Important Identified Risk #2: Angioedema	
Evidence for linking the risk to the medicine	Clinical trial data from the I/T/M Population. As for acute systemic hypersensitivity reactions, the development of angioedema is not unanticipated for an enzyme substitution therapy, and the rate of these reactions, the underlying type III mechanism and lack of other aetiological factors provide evidence that these episodes are most likely related to pegvaliase treatment.
Risk factors and risk groups	There were no specific groups identified as having a higher risk of developing angioedema.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section: 4.4, 4.8.

	PL Section: 2, 4. Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU. Additional risk minimisation measures: As angioedema may be a symptom of acute systemic hypersensitivity reactions, the same additional risk minimisation measures will apply. Educational materials for HCPs. Educational materials for Patients and Trained Observers. Patient card.
Additional pharmacovigilance activities	Observational pegvaliase exposure study (165-501).

Important Identified Risk #3: Serum sickness	
Evidence for linking the risk to the medicine	Clinical trial data from the I/T/M Population There were seven serum sickness AEs reported in the clinical trials and given the immune impact of pegvaliase resulting in CICs, this is likely to be the cause.
Risk factors and risk groups	There were no specific groups identified as having a higher risk of developing serum sickness.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section: 4.4, 4.8. PL: Section 4. Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Observational pegvaliase exposure study (165-501).

Important Identified Risk #4: Hypophenylalaninaemia	
Evidence for linking the risk to the medicine	Non-clinical trials: Single-dose toxicity studies showed that monkeys given 60 mg/kg pegvaliase exhibited morbidity between 3 and 5 days post dose due to lowering of plasma phenylalanine to non-detectable levels. Clinical trials: Approximately 46% of the patients experienced hypophenylalaninaemia.
Risk factors and risk groups	Unknown.
Risk minimisation measures	Routine risk communication: SmPC Section: 4.2, 4.4, 4.6. PL: Section 2. Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Observational pegvaliase exposure study (165-501) and, studies 165-503 and 165-504.

Important Identified Risk #5: Persistent arthralgia (≥ 6 months)	
Evidence for linking the risk to the medicine	Clinical trials: 86% of the patients experienced episodes consistent with arthralgia (including AEs of arthralgia, back pain, musculoskeletal pain, pain in extremity, and neck pain). Most of the cases were mild to moderate in severity. Persistent arthralgia (lasting at least 6 months) occurred in 21 (7%) of patients with a total of 28 episodes in the I/T/M Population.
Risk factors and risk groups	Female gender.
Risk minimisation measures	Routine risk communication: SmPC Section: 4.8. PL: Section 4. Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Observational pegvaliase exposure study (165-501).

Important Identified Risk #6: Severe injection site reactions	
Evidence for linking the risk to the medicine	Clinical trials: 93.3% of the patients experienced injection site reactions.
Risk factors and risk groups	Female gender, younger age and lower BMI.
Risk minimisation measures	Routine risk communication: SmPC Section: 4.2, 4.8. PL: Section 4. Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Observational pegvaliase exposure study (165-501).

Important Potential Risk #1: Complications of Immune complex formation resulting in end-organ damage:	
Evidence for linking the risk to the medicine	Clinical trial data from the I/T/M Population.
Risk factors and risk groups	No specific preventative measures are in place at this time.
Risk minimisation measures	Routine risk minimisation measures: None. Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Studies 165-501 and 165-503.

Important Potential Risk #2: Foetal developmental toxicity	
Evidence for linking the risk to the medicine	Non-clinical studies: Animal studies have shown toxicity associated with decreased maternal blood phenylalanine concentrations below normal levels. Uncontrolled blood phenylalanine levels before and during pregnancy were associated with an increased risk for miscarriage and major birth defects. Clinical trials: Pregnant and breastfeeding subjects were excluded from the clinical trial population however despite instructions to avoid pregnancy a few pregnancies occurred and 9 of them (including one partner pregnancy) were associated with SAEs.
Risk factors and risk groups	Not applicable.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4, 4.6. PL Section: 2. Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Study 165-504.

Important Potential Risk #3: Unpredictable immune-mediated response with off-label use in patients < 16 years	
Evidence for linking the risk to the medicine	Clinical trials: Patients < 16 years of age showed higher incidence of HAEs, acute systemic hypersensitivity reactions, injection-site reactions, and arthralgia.
Risk factors and risk groups	Female gender.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2. PL Section: 2. Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Observational pegvaliase exposure study (165-501).

Important Potential Risk #4: Acute systemic hypersensitivity reactions in patients taking other concurrent injectables containing PEG	
Evidence for linking the risk to the medicine	Clinical trials: In the clinical trials, two patients on long term use of a PEGylated medroxyprogesterone acetate product experienced hypersensitivity reactions following single doses of Palynziq.
Risk factors and risk groups	Unknown.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4. PL Section 2. Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Observational pegvaliase exposure study (165-501).

Missing Information #1: Long term safety and tolerability	
Risk minimisation measures	Routine risk minimisation measures: None. Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Observational pegvaliase exposure study (165-501).

Missing Information #2: Use in elderly patients > 65 years	
Risk minimisation measures	Routine risk minimisation measures: None. Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Observational pegvaliase exposure study (165-501).
Missing Information #3: Use in patients with pre-existing hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 5.2. Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Observational pegvaliase exposure study (165-501).

Missing Information #4: Use in patients with pre-existing renal impairment	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 5.2. Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Observational pegvaliase exposure study (165-501).

Missing Information #5: Use in breastfeeding women	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.6. PL Section: 2. Legal status: Treatment with Palynziq should be directed by physicians experienced in the management of PKU. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Observational pregnancy pegvaliase exposure study (165-504).

II.C. Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Palynziq.

II.C.2 Other studies in post-authorisation development plan

Study Short Name	Purpose of the study
165-501 A prospective observational exposure study Ongoing	**Primary Objective:** To quantify and characterize the risk of ASHRs/ anaphylaxis, angioedema, serum sickness, severe hypersensitivity reaction, persistent arthralgia (≥ 6 months), severe injection site reaction, hypophenylalaninemia (defined as a blood Phe level ≤ 30 µmol/L for a minimum of 2 consecutive values) in incident-users receiving Palynziq for the treatment of PKU in a real-world setting. **Secondary Objectives:** To quantify and characterize the risk of: • Complications of immune-complex formation or PEG accumulation resulting in end-organ damage, SAEs, severe ADRs, and ADRs leading to treatment interruption or discontinuation and/or study discontinuation in subjects receiving pegvaliase for the treatment of PKU in a real-world setting • Safety events as defined in the primary and secondary objectives in subjects receiving concomitant treatment with other pegylated (PEG) injectables during pegvaliase treatment; subjects ≥ 65 years of age during pegvaliase treatment; subjects with documented pre-existing hepatic impairment during pegvaliase treatment; subjects with documented pre-existing renal impairment during pegvaliase treatment; subjects < 16 years of age receiving pegvaliase treatment excluding Germany; and subjects with hypophenylalaninemia during pegvaliase treatment **Tertiary Objective (EU only):** To evaluate the provision of aRMM to the healthcare provider (HCP) and subject.

165-503 An immunogenicity/inflammation lab study (US) Planned	**Primary Objective:** To evaluate immunologic and inflammatory responses (immunologic testing, inflammatory markers) associated with incidence of acute systemic hypersensitivity reactions (ASHR)/anaphylaxis, angioedema, serum sickness, and severe immune-mediated adverse drug reactions (ADRs) (ie, generalized skin reactions, injection site reactions, arthralgia, and hypersensitivity) **Secondary Objectives:** • To evaluate immunologic and inflammatory responses (immunologic testing, inflammatory markers) and their effects on major-organ function (eg, kidney function) • To evaluate effect of immunologic responses on blood Phe levels
165-504 A prospective global pregnancy observational safety surveillance study Ongoing	**Primary objective** To estimate the frequency of pregnancy outcomes (eg, spontaneous abortion, fetal death/stillbirth, live birth, and termination) among subjects with PKU treated with Palyniq during pregnancy and fetal/infant outcomes (all MCMs and specifically microcephaly and congenital heart defects], FGR, SGA], low birth weight, preterm birth, failure to thrive, and developmental delays) among their offspring exposed to Palynziq during pregnancy **Secondary Objective:** • To compare the frequency of pregnancy outcomes (eg, spontaneous abortion, stillbirth, live birth, and termination) and fetal/infant outcomes (all MCMs and specifically microcephaly and congenital heart defects), FGR, SGA, low birth weight, preterm birth, failure to thrive, and developmental delays) among subjects with PKU treated with Palynziq during pregnancy and their offspring to information on those same outcomes in non-Palynziq exposed, pregnant women with PKU as described in reference literature • To examine differences in the frequency of pregnancy outcomes (eg, spontaneous abortion, stillbirth, live birth, and termination) and fetal/infant outcomes (all MCMs and specifically microcephaly and congenital heart defects, FGR, SGA, low birth weight, preterm birth, failure to thrive, and developmental delays) among subjects with PKU treated with Palynziq during pregnancy and their offspring by maternal blood Phe levels • To estimate the frequency of serious adverse events (SAEs) other than CMs in infants exposed to Palynziq during pregnancy through their first year of life • To estimate the frequency of selected outcomes in subjects with PKU treated with Palynziq during breastfeeding (low milk supply) and their infants (failure to thrive and SAEs in infants) through their first year of life

Immune tolerance induction (ITI) regimen study Planned	To assess immune mediated adverse reactions.

PART VII: ANNEXES

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ANNEX 4: Specific Adverse Drug Reaction Follow-up Forms

Specific adverse event follow-up forms are provided for the following events:

Request for Additional Information Regarding a Report associated with a Subcutaneous Injection; Form

Request for Additional Information Regarding Renal Adverse Event; Form

[redacted]

DFRF: Acute Systemic Hypersensitivity Reaction and Serum Sickness

TO:	FROM: BioMarin Pharmacovigilance 415-532-3144 drugsafety@bmrn.com

Date:

Dear ,

BioMarin Pharmacovigilance has received a report of patient who experienced an adverse event of either Acute Systemic Hypersensitivity Reaction or Serum Sickness while being treated with the following BioMarin product Palynziq® (Pegvaliase). In our effort to comply with safety reporting requirements, we would like to obtain additional information concerning this event.

If you provided the initial report for this event, it is not necessary to re-enter previously reported information unless it has changed.

Patient Initials:		Date of Birth:	
Patient Gender:	☐ Male ☐ Female	Age:	

Your office may not have provided this report. This report may have been submitted by a patient or caregiver, a sales representative, a Medical Science Liaison, our Medical Communications department, a specialty pharmacy or a Patient Support Program.

If available, we would be very grateful if you could provide the specific information required on the attached form and return the form by email, fax or mail at your earliest convenience.

Thank you

BioMarin Pharmaceutical, Inc. – Pharmacovigilance

[redacted]

[redacted]

Patient Information			
Patient Identifier:	Date of Birth/Age or Age group:	Gender at birth:	BMRN Ref #:

Reporter Information		
Name of reporter completing this form *(if other than addressee, provide contact information below)*: Name/Qualifications: Reporter's address/Organization /Department:		
Phone Number:	Fax Number:	Email Address:

Patients Suspected Drug Information						
BioMarin Drug						
Drug Name (generic or trade name)	**Lot Number**	**Indication**	**Dose Route and Frequency**	**Action taken with the drug**	**Most recent injection prior to event onset**	**Start Date Stop Date or Continuing**
					Date: Time:	Start: Stop: ☐ Continuing
					Date: Time:	Start: Stop: ☐ Continuing
					Date: Time:	Start: Stop: ☐ Continuing

Concomitant Drug (any other non-BioMarin Drug)				
Drug Name (generic or trade name)	**Dose, Route and Frequency**	**Start Date/Time**	**Stop Date/Time** (Check box next to date if Continuing)	**Indication**
		Date: Time:	☐Date: Time:	☐Pre-medication
		Date: Time:	☐Date: Time:	☐Pre-medication

[redacted]

[redacted]

		Date: Time:	☐Date: Time:	☐Pre-medication
		Date: Time:	☐Date: Time:	☐Pre-medication

The information in this form relates to an adverse drug reaction of (Please check the appropriate box – If the patient has both conditions, please complete a separate form for each):

☐ Acute systemic hypersensitivity reaction	☐ Serum Sickness

Patient's signs and symptoms: Provide severity (mild, moderate, or severe), start/stop date and time for each

System	Severity Mild, Moderate or Severe	Start Date/Time	Stop Date/Time	Outcome of the event Resolved, Resolved with sequelae, Resolving, or Not resolved
Dermatologic (e.g. flushing, urticaria, angioedema, pruritus, warmth, swelling, rash) Specify Symptom below:				
Symptom (location):				
Symptom (location):				
Symptom (location):				
Respiratory (e.g. nasal congestion, coryza, rhinorrhea, sneezing, throat tightness, wheezing, shortness of breath, cough, dyspnea, hoarseness) Specify Symptom below:				
Symptom:				
Symptom:				
Symptom:				
Cardiovascular (e.g. dizziness, weakness, syncope, chest pain, palpitations, hypotension, tachycardia) Specify Symptom below:				
Symptom:				
Symptom:				
Symptom:				

[redacted]

[redacted]

[redacted]

Gastrointestinal (e.g. dysphagia, nausea, vomiting, diarrhea, bloating, cramps) Specify Symptom below:				
Symptom:				
Symptom:				
Symptom:				
Neurologic (e.g. headache, dizziness, blurred vision, seizure) Specify Symptom below:				
Symptom:				
Symptom:				
Symptom:				
Musculoskeletal (e.g. polyarthralgia, polyarthritis) Specify Symptom below:				
Symptom (location):				
Symptom (location):				
Symptom (location):				
Other (metallic taste, feeling of impending doom, pyrexia malaise) Specify Symptom below:				
Symptom:				
Symptom:				
Symptom:				

Seriousness assessment

- Did the patient's acute systemic hypersensitivity reaction or serum sickness result in any of the following outcomes?
- If yes, please check the appropriate box and complete the further details as necessary.
- If no, please check the Non-serious box

Seriousness criterion	☐ **Non-serious**		
☐ Death	In case of death	Death date:	Autopsy:
☐ Life-Threatening			
☐ Hospitalization require/prolonged	Hospitalization dates	Admission:	Discharge:

[redacted]

[redacted]

[redacted]

☐ Persistent or significant disability or incapacity	
☐ Congenital anomaly/birth defect	
☐ Otherwise medically important	
Was pre-medication administered on the day of the event? If yes, enter in the concomitant medication's section and check pre-medication box	☐ Yes ☐ No ☐ Unknown
Where did the event occur?	☐ Home ☐ Clinic ☐ Other
Was epinephrine (adrenaline) administered?	☐ Yes ☐ No ☐ Unknown
If yes, who administered epinephrine?	☐ Patient ☐ Family Member ☐ Other
Were Emergency Medical Services called?	☐ Yes ☐ No
Did the patient go to the emergency department?	☐ Yes ☐ No
Describe clinical course (include details disregarding injection, e.g. painful injection, injection site bleeding, time to onset, treatment)	
Was the BioMarin drug re-introduced following resolution/improvement of the reported adverse event?	☐ Yes ☐ No
If yes, did the adverse event recur?	☐ Yes ☐ No
Relevant Medical History (including atopy, food or seasonal allergies)	

[redacted]

[redacted]

[redacted]

Relevant Laboratory/Diagnostic Data		
Test	**Date**	**Result**

[redacted]

[redacted]

Request for Additional Information Regarding a Report of an Adverse Event

TO:	FROM: BioMarin Pharmacovigilance 415-532-3144 drugsafety@bmrn.com

Date:

Dear ,

BioMarin Pharmacovigilance has received a report of a patient who experienced a Renal adverse event while being treated with the following BioMarin product: Palynziq (Pegvaliase). In our effort to comply with safety reporting requirements, we would like to obtain additional information concerning this event.

If you provided the initial report for this event, it is not necessary to re-enter previously reported information unless it has changed

Patient Initials:		Date of Birth:	
Patient Gender:	☐ Male ☐ Female	Age:	

Your office may not have provided this report. This report may have been submitted by a patient or caregiver, a sales representative, a Medical Science Liaison, our Medical Communications department, a specialty pharmacy or a Patient Support Program.

If available, we would be very grateful if you could provide the specific information required on the attached form and return the form by email, fax or mail at your earliest convenience.

Thank you

BioMarin Pharmaceutical, Inc. – Pharmacovigilance

[redacted]

[redacted]

[redacted]

Patient Information			
Patient Identifier:	Date of Birth/Age or Age group:	Gender at birth:	BMRN Ref #:

Patient's Relevant Drug Exposure History						
BioMarin Drug						
Drug Name (generic or trade name) Route	**Lot Number Dose and Frequency**	**Route**	**Indication**	**Most recent dose prior to event onset**	**Start Date/Stop Date or continuing** (Check box next to start if Continuing)	**Is there a causal relationship between the BioMarin Drug and the Renal Event**
				Date: Time:	☐Start: Stop:	☐ Yes ☐ No
				Date: Time:	☐Start: Stop:	☐Yes ☐No
				Date: Time:	☐Start: Stop:	☐Yes ☐No

Concomitant Drug (any other non-BioMarin Drug)				
Drug Name (generic or trade name)	**Dose, Route and Frequency**	**Start Date/Time**	**Stop Date/Time** (Check box next to date if Continuing)	**Indication**
		Date: Time:	☐Date: Time:	☐Pre-medication
		Date: Time:	☐Date: Time:	☐Pre-medication

[redacted]

[redacted]

[redacted]

		Date: Time:	☐ Date: Time:	☐ Pre-medication
		Date: Time:	☐ Date: Time:	☐ Pre-medication
Renal Adverse Event				
Event Term:				
Event Seriousness: ☐ Yes ☐ No **If yes:** ☐ Fatal ☐ Medically significant ☐ Life Threatening ☐ Congenital Anomaly ☐ Hospitalized ☐ Significant Disability		Event Severity: ☐ Mild ☐ Moderate ☐ Severe		
Event Start Date:		Event Stop Date:		
Describe clinical course:				
Patient's pertinent symptoms (i.e.: Edema, rash, frothy urine, hematuria, dehydration):				
Treatment for the event:				

[redacted]

[redacted]

[redacted]

Relevant Medical History (including prior renal disease):
Does the subject have risk factors for renal impairment (i.e.: hypertension, diabetes, obesity, medication use, etc.)? ☐ Yes ☐ No **If yes, please list them:**
Was the patient referred to a nephrologist for further evaluation? ☐ Yes ☐ No **If yes, and If a consultation report is available; please attach. Otherwise, please summarize findings and recommendations below.**

Relevant Laboratory Data (Urine and Serum)		
Test	Date	Result

[redacted]

[redacted]

Relevant Diagnostic Imaging or Biopsy Results (if Yes, and a report is available, please attach)		
Test	Date	Result
Renal US performed: ☐ Yes ☐ No		
Renal biopsy performed? ☐ Yes ☐ No		
☐ Other		

Name of reporter completing this form (if other than addressee, provide contact information below):		
Name:		
Phone Number:	Fax Number:	Email Address:

[redacted]

[redacted]

ANNEX 6: Details of Proposed Additional Risk Minimisation Activities

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