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.