CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OTHER REVIEW(S)

Department of Health and Human Services
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Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates
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Date:	May 22, 2018
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Subject:	Active Risk Identification and Assessment (ARIA) Sufficiency Memo for Pregnancy Safety Concerns
Drug Name:	Palynziq (pegvaliase)
Application Type/Number:	BLA 761079
Applicant/sponsor:	Biomarin Pharmaceutical, Inc.
OSE RCM #:	2017 - 1327

A. Expedited ARIA Sufficiency Template for Pregnancy Safety Concerns

1. BACKGROUND INFORMATION

1.1. Medical Product

Palynziq (pegvaliase) is an enzyme substitution therapy indicated to reduce blood phenylalanine (Phe) concentrations in adult patients with phenylketonuria (PKU) who have uncontrolled blood phenylalanine concentrations > 600 µmol/L on existing management. Palynziq substitutes for the deficient PAH enzyme in patients with PKU by providing an alternate pathway for Phe breakdown via the enzymatic conversion of Phe to trans-cinnamic acid (t-CA) and ammonia, both excreted in the urine. Palynziq is administered daily as a subcutaneous injection through a single-dose prefilled syringe. The proposed dosing follows an induction, titration, and maintenance (I/T/M) dosage regimen by which the dose is slowly increased over a period of a few weeks. The Applicant proposes that a patient should stay at 20 mg daily for 24 weeks and the dose may be increased to 40 mg daily based on individual patient response (Phe concentration) and tolerability. If a patient does not achieve at least a 20% reduction in blood Phe concentration from their pre-treatment baseline after an additional 16 weeks of treatment with 40mg daily, then the product should be discontinued.

1.2. Describe the Safety Concern

Elevated maternal blood Phe concentration during early pregnancy is teratogenic and may result in Phe embryopathy. The embryopathic effects of elevated Phe levels during pregnancy in maternal PKU include growth retardation, microcephaly, psychomotor retardation, and congenital heart defects.[1] Available data from the Maternal Phenylketonuria Collaborative Study on 468 pregnancies and 331 live births in PKU-affected women demonstrated that uncontrolled phenylalanine concentrations above 600 micromol/L are associated with an increased risk for miscarriage, major birth defects (including microcephaly, major cardiac malformations), intrauterine fetal growth retardation, and future intellectual disability with low IQ. To reduce the risk of hyperphenylalaninemia-induced teratogenic effects, target blood phenylalanine concentrations of 120 to 360 micromol/L should be maintained for 3 months before conception and throughout pregnancy.[2]

There is limited data on the developmental effects of Palynziq use in pregnant woman. Based on the 120-day safety update report and cumulative pregnancy data, 10 female subjects became pregnant during treatment, with information on timing of exposure missing.[1] In summary, the 10 pregnancies included 3 therapeutic/induced abortions, 1 missed abortion, 1 stillbirth, 1 normal delivery, 1 delivery of an infant with transient systolic murmur which resolved without intervention, and 3 ongoing at the time of the Safety Update data cutoff. As described above, it is known that pregnant patients with PKU are at increased developmental risk with elevated Phe levels, so causality can be difficult to establish with limited subject details and lab data. In addition,

[1] Biologic License Application (BLA) Multi-Disciplinary Review and Evaluation. BLA 761079 Palynziq (pegvaliase-pqpz). Accessed May 16, 2018. DARRTS Reference ID: Pending.

[2] Palynziq product label. Revised May 2018. DARRTS Reference ID: Pending.

9 female partners of male study subjects (partner pregnancies) became pregnant during treatment.[1] Two male subjects have female partners who were pregnant twice, for a total of 11 partner pregnancies. In the 11 partner pregnancies, 6 pregnancies had a reported normal outcome. The remaining 5 partner pregnancies included 1 delivery of an infant with neonatal respiratory distress who was discharged after receiving 2 days of respiratory support, 1 delivery with no additional data, 2 with unknown outcomes of the delivery, and 1 ongoing at the time of the Safety Update data cutoff.

Embryofetal malformations (of the skeleton, kidneys, lungs, and eyes) and embryofetal toxicity (increased resorptions, reduced fetal weight) were observed in the offspring of pregnant rabbits (without PKU) treated with Palynziq in the nonclinical program at a dosage which was 7.5 times higher than the maximum recommended daily dose; these adverse fetal effects in the rabbit study were associated with strong signs of maternal toxicity, including marked reductions in weight gain and food consumption, and death.[1] A reproduction study in rats (without PKU) demonstrated an increase in skeletal variations, but with no malformations observed. The effects occurred at 4.2 times the maximum recommended daily dose. In a pre-/post-natal development study in rats (without PKU), Palynziq produced decreases in survival of offspring when administered daily at 19.4 times the maximum recommended daily dose. The effects on rat embryo-fetal and post-natal development were associated with maternal toxicity. The significance of these findings for humans remains unknown.

It is discussed in the label that Palynziq may cause fetal harm with supporting animal and human data, although the data is limited and insufficient to determine a drug-associated risk of adverse developmental outcomes.[2] Further evaluation in the post-marketing setting is necessary for appropriate education of patients and prescribers when considering the use of Palynziq during pregnancy. A post-approval pregnancy monitoring program has been proposed to further evaluate safety risks associated with Palynziq treatment in pregnant women with PKU and their offspring. In addition, the product label includes the following language: "*There is a pregnancy surveillance program for Palynziq. If Palynziq is administered during pregnancy, or if a patient becomes pregnant while receiving Palynziq or within one month following the last dose of Palynziq, healthcare providers should report Palynziq exposure by calling 1 866 906 6100*."

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected

☐ No approved indication, but practitioners may use product off-label in pregnant women

☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized

☒ No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty.
☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review).

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☐ Pregnancy registry with internal comparison group
☐ Pregnancy registry with external comparison group
☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☐ Electronic database study with chart review
☐ Electronic database study without chart review
☒ **Other, please specify**: A Pregnancy Monitoring Program is being considered to further evaluate a nonspecific safety concern associated with Palynziq treatment in pregnant women with PKU and their offspring.

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☒ Study Population
☐ Exposures
☒ Outcomes
☒ Covariates
☒ Analytical Tools

For any checked boxes above, please describe briefly:

Study Population and Outcomes and Covariates: ARIA is not sufficient to identify the study population (babies that experienced in utero exposure or postpartum exposure through lactation) because the mother and baby records are not currently linked in Sentinel. Thus, the exposure corresponding to the mother and potential outcomes corresponding to the infant cannot be connected. This lack of linkage between mother and baby records renders ARIA insufficient for both the study population and outcome identification.

Covariates: ARIA is not sufficient to capture maternal blood phenylalanine concentrations during pregnancy making it impossible to examine the associations between Palynziq treatment, blood Phe levels and adverse outcomes in the pregnant women and their offspring.

Analytical Tools: ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been tested for birth defects and other pregnancy

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