Considerations for the use of pegvaliase in adolescents with phenylketonuria

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Background

- Phenylketonuria (PKU) is an autosomal recessive disorder caused by phenylalanine hydroxylase deficiency, resulting in elevated phenylalanine (Phe) levels in the blood and brain, which can impair neurocognitive function and quality of life (QOL), and requires lifelong management[1,2]
- Adolescence presents unique challenges for individuals with PKU, as increasing independence and social pressures often lead to reduced adherence to medical nutrition therapy (MNT), with subsequent elevations in blood Phe that may negatively affect executive function and attention
- Pegvaliase, an enzyme substitution therapy recently approved in the United States (US) for adolescents (≥12 years) with PKU and blood Phe >600 µmol/L, has shown clinically meaningful reductions in blood Phe versus diet only, with safety and efficacy comparable with adults[4,5,6]
- In collaboration with an expert panel, we describe key considerations for pegvaliase use in adolescents with PKU

Methods

- Eleven US PKU experts convened in April 2025 to discuss pegvaliase use in adolescents, focusing on patient selection, clinical differences from adults, and management insights

Results

- Collectively, the 11 advisors managed around 850 individuals with PKU, including about 300 adolescents (12–17 years)
  - Eighty percent of advisors managed individuals with pegvaliase for ≥5 years
  - Most advisors were involved in the phase 3 PEGASUS adolescent trial and some had clinical experience using pegvaliase

Figure 1. Goals, indicators of treatment success, and challenges for adolescents with PKU identified by the advisors

Key goals	Indicators of treatment success	Key challenges
• Achieve and maintain optimal blood Phe control • Protect neurocognitive and mental health • Promote self-management skills	• Growth and development • Academic success • Quality of life • Engagement in medical care	• Disengagement from PKU care • Nonadherence to treatment • Impact of elevated Phe levels • Educating patients and managing expectations • Transitioning to adulthood

Figure 2. Key treatment-related considerations and benefits for pegvaliase use in adolescents identified by the advisors

Treatment challenges: Pegvaliase is an important treatment option for those struggling with adherence to MNT and may prevent long-term complications while also potentially improving QOL and lifelong patient outcomes

Treatment motivation: Understanding the adolescent's motivations is critical, as it allows treatment to be individualized and can uncover how previous treatment experiences reinforced the burden of PKU management

Treatment suitability: Given the potential of diet liberalization in responders, all adolescents interested in pegvaliase treatment should be considered, with additional support for those with needle phobia or difficulty recognizing serious adverse events (AEs) such as anaphylaxis

Support needs: While clinical goals remain the same for adolescents and adults, adolescents may benefit from additional hands-on training for self-injection and epinephrine administration; younger adolescents may require more familial support, whereas older adolescents could benefit from greater independence and encouragement to develop self management skills

Patient priorities: Adolescents may prioritize social acceptance, lack of interruptions to school, and social activities. These should be considered when individualizing treatment

Patient-driven decision-making: Emotional maturity and developmental readiness, without parental pressure, should drive the decision to initiate pegvaliase. This fosters a sense of ownership that may promote stronger engagement and sustained adherence

Treatment initiation and dose adjustment insights

- Healthcare professionals (HCPs) should provide an overview of pegvaliase treatment timelines, including potential challenges, AEs and anticipated outcomes
- Starting pegvaliase in adolescence can support critical developmental milestones, foster greater independence and facilitate the transition to adulthood; voluntary initiation may improve adherence, and emotional maturity is a key factor
- Pegvaliase dosing in adolescents should be flexible around major life events to reduce AEs and avoid interruptions. Adjust titration during less demanding times, such as summer break, to limit academic and social disruption

Diet management insights

- Open, nonjudgmental communication between healthcare providers and patients allows for realistic dietary expectations and supports patients' desired eating habits during pegvaliase treatment
- Personalized and ongoing adjustments to diet and protein intake are recommended to accommodate growth and lifestyle

Navigating pegvaliase treatment in adolescence

- Advisors noted that pegvaliase management is similar for adolescents and adults, except that younger teens (especially ages 12–14) may require more caregiver support
- As adolescents mature (15–17 years), direct patient–provider communication becomes crucial to fostering autonomy
- Management differences arise due to varying maturity levels. **Table 1** outlines the key recommendations by age group

Table 1. Age-related considerations with pegvaliase treatment*

	12–14 years	15–17 years
Decision to start treatment	▪ Ensure caregiver support to set expectations and recognize when adjustments are necessary ▪ Assess maturity, adherence, and cognitive factors ▪ Consider transition periods (eg, starting high school)	▪ Initiate discussions on sexual health, contraception, and maternal PKU early ▪ Consider timing of major milestones (eg, graduation, college transition)
Initiating treatment	▪ Initial caregiver support for self-injection may help to develop confidence and competence	▪ Prepare for independence (eg, requesting prescription refills on time) ▪ Involve trusted individuals with injection education and patient support to reinforce adherence
Maintenance phase	▪ Emphasize monitoring Phe levels and dietary intake ▪ Adapt injection scheduling to events (eg, camps, holidays)	▪ Prioritize Phe monitoring over detailed diet records ▪ Limit diet recordkeeping to periods when dietary adjustments are necessary
AE management	▪ Share emergency contact information with school and peers ▪ Use diary to track premedication adherence and AE occurrence	▪ Encourage routine-building strategies (eg, pillbox for premedications) ▪ Prepare a medical kit with supplies and on-demand medications for independent living/college
Efficacy assessment, dietary adjustments, and dose changes	▪ Simplify diet tracking using apps or other tools ▪ Foster open discussion about dietary intake and goals, injection routines, and evolving nutritional needs	▪ Monitor changes in mood, behavior, and cognition with stabilizing Phe levels ▪ Discuss school performance and new food preferences ▪ Provide education to support a healthy, balanced diet

*Age-related considerations are not mutually exclusive, and guidance for adolescents aged 12–14 years may still apply to adolescents age 15–17 years

Education and support

- Individualized management approaches can help foster adolescent independence, reinforce routine attendance to clinic appointments, and strengthen communication with the clinic team, supporting the transition to adult care
- Frequent touchpoints can support adolescents during initiation, titration, and AE management[7,8]
- Engaging educational materials such as interactive Q&As and videos can support comprehension and adherence
- BioMarin clinical coordinators can partner to reinforce injection training and AE management (eg, epinephrine readiness)

The significance of pegvaliase treatment for adolescents with PKU

Figure 3. Observed benefits and improvements of pegvaliase treatment

- Focus, executive function, & academic/job performance
- Ability to liberalize diet & increase intact protein intake
- QOL including greater independence & autonomy
- Mood, behavior, & symptoms of depression and anxiety
- Relationships
- Physical growth and muscle mass

Figure 4. Why pegvaliase is important as a treatment option for adolescents

Empowers patients with more choices and an opportunity to liberalize diet

Offers an opportunity for better Phe control at a **critical time** when standard of care often fails

Can support lifestyle choices and individualized nutritional needs for growth and sports during key developmental stages

Conclusions

- Adolescents will benefit from customized management approaches that support their unique needs and provide opportunities for independence and treatment engagement
- Treatments that require dietary restriction are challenging and often insufficient for individuals living with PKU. Pegvaliase can help manage elevated blood Phe in adolescents, thereby maintaining neurocognitive functioning and QOL
- Advisors identified that the goals of pegvaliase treatment are to improve everyday functioning, enable higher educational achievement, and help adolescents reach their full potential
- Pegvaliase may offer adolescents the opportunity to foster independence and take ownership of their disease management. This includes dietary liberalization, actively evaluating their individual response to treatment, and communicating these experiences to their metabolic team and caregivers

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Abbreviations

AE, adverse event; **HCP,** healthcare professional; **MNT,** medical nutrition therapy; **Phe,** phenylalanine; **PKU,** phenylketonuria; **Q&A,** question and answer; **QOL,** quality of life; **US,** United States

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