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ACMG THERAPEUTICS BULLETIN

Sepiapterin approved for children and adults with phenylketonuria (PKU): A therapeutics bulletin of the American College of Medical Genetics and Genomics (ACMG)

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Background

Phenylketonuria (PKU), also known as phenylalanine hydroxylase (PAH) (HGNC:8582) deficiency, is an autosomal recessive disorder of phenylalanine (Phe) metabolism due to deficiency of the enzyme PAH, which normally converts Phe to tyrosine (Tyr) (HGNC:12442) in the presence of the cofactor tetrahydrobiopterin (BH4).[1] Deficient PAH activity results in elevated blood and brain Phe concentrations, resulting in profound neurocognitive delays if left

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untreated. PKU represents a spectrum of disease severity correlating to residual enzyme activity, from mild hyperphenylalaninemia to classic PKU, the most severe form. Clinical symptoms of untreated classic PKU include intellectual disability, microcephaly, epilepsy, neuropsychiatric symptoms, and hypopigmentation of the skin, hair, and eyes due to deficient Tyr, which is a precursor of melanin. Newborn screening for PKU has been implemented in the United States and many countries worldwide, allowing for early diagnosis and presymptomatic treatment. When diagnosed through newborn screening and treated from infancy, affected individuals can achieve normal neurocognitive development as long as they maintain plasma Phe levels within treatment range.

Management and Treatment

Evidence-based guidelines for the diagnosis and treatment of PKU have been well established.[1–6] The American College of Medical Genetics and Genomics published comprehensive evidence-based guidelines for PAH deficiency diagnosis and management in 2014, with a systematic evidence review in 2023[2] and an updated clinical guideline in 2025.[3] The mainstay of treatment for PKU is dietary Phe restriction and adjunctive medication when appropriate to maintain plasma Phe levels within the range of 120 to 360 μmol/L (2-6 mg/dL) to allow for normal growth and development. This is achieved primarily through a Phe-restricted diet with limited natural protein intake, Phe-free amino acid formula supplemented with Tyr, and low-protein medical foods. Approved pharmacologic therapies for PKU include sapropterin (Kuvan or generic),[7] an orally administered synthetic derivative of BH4 effective in some patients with PKU (primarily milder phenotypes), and pegvaliase (Palynziq),[8] a subcutaneously injected pegylated phenylalanine ammonia-lyase approved for adults aged 18 years and older in the United States with inadequate blood Phe control on existing management.

Newly Approved Therapy

Indication and approved treatment population

Sepiapterin (Sephience) was approved by the FDA in July 2025 for the treatment of patients with sepiapterin-responsive PKU ≥ 1 month of age, to be used in conjunction with a Phe-restricted diet.[9,10] Sepiapterin was approved by the European Commission in June 2025.[11] Patients should undergo a 14-day trial to determine sepiapterin responsiveness (≥30% reduction in blood Phe) before long-term treatment. Sepiapterin is administered orally once daily with food, and starting dosages are age and weight dependent.

Mechanism of action

Sepiapterin is a synthetic form of a naturally occurring precursor of BH4, an essential cofactor and molecular chaperone for PAH.[12] It is actively transported into cells and converted to BH4 via the pterin salvage pathway, which increases residual PAH activity to convert Phe to Tyr and lower blood Phe concentration.

Outcomes and efficacy

The efficacy of sepiapterin was evaluated in 2 clinical trials. Approval was based on safety and efficacy results from the placebo-controlled phase III APHENITY trial (NCT05099640) and its long-term extension study (NCT05166161).[9,13]

The APHENITY trial was a phase 3, international, randomized, anonymized, 2-part, placebo-controlled trial that enrolled 157 participants (age range 1-61 years) with PKU and blood Phe ≥ 360 μmol/L. In part 1 of the trial, participants ($n = 156$) underwent a 14-day open-label trial to determine sepiapterin responsiveness (≥15% reduction in blood Phe from baseline) before continuing onto part 2 ($n =$ 110 participants; 56 in the sepiapterin group, 54 in the placebo group), a 6-week randomized, placebo-controlled dose escalation phase at 20, 40, and 60 mg/kg per day. The study's primary endpoint was the mean change in blood Phe concentration from baseline to week 6 in part 2 of the trial. Secondary endpoints included the proportion of participants with baseline blood Phe concentration of ≥600 μmol/L who achieved Phe < 600 μmol/L and the proportion of those with baseline blood Phe concentration of ≥360 μmol/L who achieved Phe < 360 μmol/L at week 6, as well as safety, tolerability, and sepiapterin dose-response pharmacokinetics.[13]

Overall, 73% (114/156) participants were found to be responsive to sepiapterin, and 66% (103/156) showed ≥30% reduction in blood Phe from baseline, including 46% (16/35) of participants with classic PKU.

The primary endpoint was met based on efficacy analysis in the 98 participants with ≥30% reduction in blood Phe from baseline in part 1 of the study (49 in the sepiapterin group and 49 in the placebo group). After 6 weeks of treatment, participants on sepiapterin showed a 63% reduction in blood Phe (−410.1 μmol/L, SD 204.4) compared with 1% on placebo (−16.2 μmol/L, SD 198.6), which was a statistically significant difference (least squares mean change from baseline between the groups of −395.9 μmol/L, $P < .0001$).

After six weeks of sepiapterin treatment while maintaining consistent Phe intake, 84% (37/44) of participants with baseline Phe > 360 μmol/L achieved a Phe level of ≤ 360 μmol/L and 22% (11/49) reached a blood Phe within normal range (35-120 μmol/L). Although efficacy was demonstrated across all subgroups (classic PKU, BH4 nonresponders, and participants previously on sapropterin),

participants with classic PKU had the lowest response rate (46%).

In the long term, open-label extension trial, 169 participants (65 adults and 104 pediatric) as of data cut on June 30, 2024 were treated with sepiapterin. Continued efficacy was demonstrated in participants ≤ 2 years of age, with 66% (6/9) showing ≥30% absolute reduction in blood Phe from baseline to weeks 1 and 2 of −125 umol/L (SD 265.9 umol/L).[13,14]

Adverse effects and toxicity

Sepiapterin was generally well tolerated in pediatric and adult participants with PKU in the phase II and III clinical trials. The most common adverse reactions with sepiapterin (≥2% and greater than placebo) were diarrhea, headache, upper respiratory infection, abdominal pain, hypophenylalaninemia, feces discoloration, and oropharyngeal pain.

Individuals on sepiapterin may be at increased risk of bleeding events (eg, superficial hematomas, heavy menstrual bleeding, and prolonged bleeding). One participant in phase 2 of the APHENITY trial discontinued sepiapterin due to nontraumatic superficial hematomas and prolonged bleeding, which started 15 days after starting treatment and recurred 2 days after rechallenging at a lower dose of sepiapterin.[9] The participant had normal blood counts and coagulation studies at the time of the bleeding. Patients on sepiapterin are also at risk for hypophenylalaninemia; therefore, frequent blood phenylalanine monitoring with dose and dietary modifications is recommended to prevent adverse impact on growth.

Sepiapterin has potential interactions with several drugs. Sepiapterin increases the availability of Tyr, a precursor of levodopa; therefore, concomitant administration with levodopa may cause seizures, overstimulation, or irritability. Participants should be monitored for changes in neurologic status when on both drugs. Individuals on sepiapterin should avoid concomitant use of folate synthesis dihydrofolate reductase (HGNC:2861) inhibitors and sepiapterin reductase (HGNC:11257) inhibitors, which may reduce sepiapterin metabolism to BH4. If concomitant use is unavoidable, blood Phe levels should be monitored. Concomitant use of sepiapterin and drugs that affect nitric oxide-mediated vasorelaxation (eg, PDE-5 inhibitors) may induce hypotension, and blood pressure should be monitored.[9]

Sepiapterin does not carry any boxed warnings for prescribers.

Additional Considerations

A limitation of the APHENITY study was that the randomized, placebo-controlled part of the trial was only 6 weeks in duration. In addition, there are no adequate human data on the use of sepiapterin during pregnancy or lactation; animal data are limited and use should involve individualized risk-benefit assessment given the known risks of uncontrolled maternal hyperphenylalaninemia and the lack of data in breastfed infants.

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Conflict of Interest

All workgroup members receive salary for providing clinical services that may be relevant to the content of this document in either the laboratory or patient care setting at their listed affiliations. The following workgroup members have additional conflicts of interest: Irene J. Chang receives clinical research funding unrelated to this medication and disorder from Denali Therapeutics, JCR Pharmaceuticals, Sanofi, Ultragenyx, Spur Therapeutics, and serves on the medical advisory board of Chiesi USA and Spruce Biosciences. Danny E. Miller is on scientific advisory boards at Basis Genetics and Inso Biosciences and has received research support from Oxford Nanopore Technologies, PacBio, Illumina, GeneDx, and BioMarin and stock options in MyOme, Basis Genetics, and Inso Biosciences.

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