FDA Approves Sepiapterin for Adults, Children Living With Phenylketonuria

Key Takeaways

- Sepiapterin is approved for PKU treatment, addressing unmet needs in managing phenylalanine buildup and preventing neurological damage.
- The drug enhances phenylalanine hydroxylase activity and corrects enzyme misfolding, effectively reducing Phe levels in patients.
- Phase 3 APHENITY trial data showed significant dietary liberalization and increased protein intake while maintaining controlled Phe levels.
- Over 70% of patients in the trial had a genotype-phenotype consistent with classical PKU, aiding in diagnosis and treatment planning.

Sepiapterin treatment allowed for patients to liberalize their diet while reaching or exceeding recommended daily protein allowances in patients living with phenylketonuria.

The FDA has granted regulatory approval to sepiapterin (Sephience; PTC Therapeutics) for the treatment of adults and children living with phenylketonuria (PKU), a rare, inherited metabolic disease that impacts the brain and leads to a buildup of the amino acid phenylalanine (Phe), according to a news release from PTC Therapeutics.1,2

Importantly, the approval includes broad labeling that features an indication for the treatment of hyperphenylalaninemia (HPA) in adult and pediatric patients aged 1 month and older with sepiapterin-responsive PKU, the news release stated.1

"We are excited to have reached this important milestone for those affected by PKU," Matthew B. Klein, MD, CEO of PTC Therapeutics, said in a news release. "The broad labeling reflects the potential of [sepiapterin] to meet the significant unmet need of PKU patients."1

What is Phenylketonuria, and How Does Sepiapterin Combat It?

Phenylketonuria is a rare condition caused by a defect in the gene that creates an enzyme that can break down Phe, which is a critical amino acid that is found in all proteins and many foods. If left poorly managed or untreated, levels of Phe can build up to harmful levels in the body. This buildup can cause severe and irreversible disabilities, including permanent intellectual disability, delayed development, memory loss, and seizures, among other brain health complications.2

Although newborns with PKU don't often present with symptoms, they can progress over the course of multiple years. Critically, the damage caused by toxic levels of Phe in the early years

of life is irreversible. Being a rare, genetic disease, there remains a critical need for novel, effective, and safe treatments to combat the toxic levels of Phe buildup and improve patient quality of life.1,2

Sepiaterin, an oral formulation of synthetic sepiapterin, features a dual mechanism of action that heightens activity of the phenylalanine hydroxylase (PAH) enzyme. Additionally, sepiapterin contains an independent, pharmacological chaperone effect, which corrects MAH misfolding to increase enzyme function. The approval of sepiapterin will increase available options for this patient population.1,2

"Through this dual mechanism of action, sepiapterin effectively reduces blood phenylalanine (Phe) levels and has the potential to treat a broad range of PKU patients," investigators from PTC Therapeutics said in the news release.3

Phase 3 APHENITY Data Indicate Effectiveness of Sepiapterin at Reducing Phe Levels

Key data on sepiapterin were presented at the 2025 American College of Medical Genetics and Genomics Annual Clinical Genetics Meeting, providing clinicians and pharmacists a wide breadth of information on the significant benefits of the agent. The data stemmed from the phase 3 APHENITY (NCT05099640) clinical trial and its companion open-label extension study.3,4

According to investigators from PTC Therapeutics, over 97% of individuals participating in the Phe tolerance protocol of APHENITY's open-label extension demonstrated the ability to liberalize their diet while on sepiapterin treatment, with a mean protein intake increase of 126%. Furthermore, 66% of subjects that participated in the Phe tolerance sub-study either reached or exceeded the age-adjusted recommended daily allowance of protein intake for an individual without PKU, while simultaneously maintaining control of blood Phe levels.3

Furthermore, according to a genetic variant analysis of subjects enrolled in the APHENITRY trial, over 70% of patients had a genotype-phenotype value consistent with the presentation of classical PKU, providing clinicians with important insights that could serve as useful when diagnosing patients with PKU and considering their tolerability for sepiapterin.3

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