FDA Approves Leucovorin Calcium as First Treatment for Cerebral Folate Transport Deficiency Due to FOLR1 Variant

Key Takeaways

1. FDA clearance for Wellcovorin is restricted to genetically confirmed biallelic FOLR1 variants, reflecting a precision-indication approach despite prior policy attention to broader autism symptom use.
2. Evidence base comprised real-world, published case data: 46 treated patients overall, with 24/27 (89%) showing improvement on oral leucovorin, spanning infancy through adulthood.
3. Mechanistic rationale centers on folinic acid CNS entry through RFC, bypassing dysfunctional FRα, with treatment goals tied to restoring CSF 5-MTHF and mitigating neurological decline.
4. Earlier initiation, including presymptomatic treatment of younger siblings after a family diagnosis, appears to improve neurodevelopmental outcomes and may prevent severe manifestations.
5. Pharmacists should distinguish leucovorin from folic acid; folic acid is discouraged in CFD-FOLR1 due to potential competitive binding effects, and diagnosis requires FOLR1 genotyping plus CSF 5-MTHF.

The approval is significant for a condition that is estimated to affect fewer than 1 in 1 million individuals.

The FDA has granted expanded approval to leucovorin calcium tablets (Wellcovorin; GlaxoSmithKline) for the treatment of cerebral folate transport deficiency in patients with a confirmed variant in the folate receptor 1 (FOLR1) gene (CFD-FOLR1), marking the first FDA-approved therapy for this ultra-rare neurological condition.[1]

What is Cerebral Folate Transport Deficiency?

CFD-FOLR1, also known as FOLR1-related cerebral folate transport deficiency (FOLR1-CFTD), is an autosomal recessive genetic disorder caused by pathogenic variants in the FOLR1 gene, which encodes the folate receptor alpha (FRα) protein responsible for transporting folate across the blood–brain barrier. Without adequate folate in the central nervous system, individuals who are affected experience progressive neurological deterioration, including developmental delays and regression, intellectual disability, seizures, ataxia, and movement disorders, often presenting in infancy after an initial period of normal motor development. The condition is estimated to affect fewer than 1 in 1 million individuals, making it one of the rarest genetic conditions known.[2-4]

“Today’s approval represents a significant milestone for patients living with cerebral folate transport deficiency due to the FOLR1 variant, a rare genetic condition that has had no FDA-

approved treatment options until today," Marty Makary, MD, MPH, FDA commissioner, said in a news release.[1]

Data Supporting FDA Approval for Leucovorin Calcium

The approval is notable for its unconventional evidentiary basis. Rather than requiring data from a traditional randomized controlled trial, the FDA conducted a systematic review of published literature from 2009 to 2024, including case reports with patient-level data. The agency identified 46 patients with CFD-FOLR1 who received leucovorin across various administration routes. Among the 27 patients treated with oral leucovorin alone, 24 (89%) demonstrated clinically meaningful neurological improvements, including reductions in seizure frequency or severity and improvements in motor function, communication, and/or behavior, while the remaining 3 showed either no change or disease progression. Patients ranged from approximately 2 months to 33 years of age at treatment initiation.[1,4]

What are Leucovorin Calcium Tablets' Implications?

Leucovorin calcium, which is also known as folinic acid or 5-formyltetrahydrofolate, is a reduced, active form of folate that can enter the central nervous system through the reduced folate carrier (RFC), bypassing the dysfunctional FRα in patients with FOLR1 mutations.[5]

The objective of therapy is to normalize 5-methyltetrahydrofolate (5-MTHF) levels in the cerebrospinal fluid (CSF). Clinical evidence suggests that outcomes are significantly better when treatment is initiated early in life and that treatment of asymptomatic or mildly symptomatic younger siblings following a family diagnosis may prevent or substantially mitigate neurocognitive manifestations of the disorder.[2]

The National Organization for Rare Disorders notes that oral leucovorin calcium has been shown to improve symptoms and stabilize CSF 5-MTHF levels, with no serious adverse effects recorded during treatment.[3]

FDA Narrows Approval Despite Earlier Autism Attention

The approval comes months after the Trump administration drew significant attention to leucovorin in September 2025, when FDA Commissioner Makary announced an initiative to make the drug available for autism symptoms more broadly. Following a comprehensive review of available evidence, however, the FDA determined that sufficient data existed only to support approval for the genetically confirmed CFD-FOLR1 subpopulation. Senior FDA officials stated that while the data were strong enough to support approval in this specific population, there was insufficient evidence to establish efficacy for autism more broadly. The American Academy of Pediatrics has maintained that evidence supporting leucovorin use in children with autism is currently limited and that larger, independent trials are needed.[1,4-6]

What Pharmacists Should Know About Leucovorin vs Folate Supplements

For pharmacists, it is important to distinguish leucovorin from over-the-counter folate supplements. Leucovorin is a prescription medication that, unlike standard folic acid, can cross the blood–brain barrier through the RFC pathway. Folic acid is not recommended in CFD-FOLR1, as it may bind tightly to the defective FOLR1 receptor and potentially interfere with any residual function. Diagnosis requires molecular genetic testing to confirm biallelic pathogenic FOLR1 variants, along with CSF 5-MTHF measurements to assess folate levels in the central nervous system.[2]

"The approval of leucovorin for FOLR1-related CFD-FOLR1 demonstrates the FDA's commitment to rapidly identifying effective treatments for ultra-rare diseases while maintaining the same evidentiary standards for approval," Tracy Beth Hoeg, MD, PhD, acting director of the FDA's Center for Drug Evaluation and Research, said in the news release. "It also provides a good example of how observational or 'real world' evidence can lead to an FDA approval when the product is shown to provide clear clinical benefit compared with what is seen with the natural history of the disease."[1]

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