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Press Release

Regarding FDA's Approval of Leucovorin as a Treatment for Cerebral Folate Deficiency

FDA's Recent Approval

On March 9, 2026, the U.S. Food and Drug Administration (FDA) announced the approval of Wellcovorin for the treatment of Cerebral Folate Deficiency (CFD).[1] This is an important first step for FDA to address the critical needs of patients with rare diseases based on common sense and real world evidence (RWE). The approval of leucovorin, a reduced folate and the active ingredient of Wellcovorin, is of extreme interest to the larger autism community for which folate therapies are emerging as important treatment options. We are very encouraged by the Agency's open-mindedness to approve evidence-based therapy for this rare disease. The traditional well-controlled studies needed to adequately support a new drug approval for rare conditions remains difficult, if not impossible. For this reason, the FDA's approval of Wellcovorin for this rare disease is an important first step in making treatments available to patients with impaired folate metabolism.

About Cerebral Folate Deficiency (CFD)

Cerebral folate deficiency (CFD) is a neurological disorder characterized by low concentrations of 5-methyl-tetrahydrofolate (5-MTHF) in the cerebrospinal fluid (CSF), despite normal systemic folate levels. Clinical manifestations typically appear in early childhood and sometimes include developmental delay or regression, seizures, movement disorders (such as ataxia or dystonia), hypotonia, demyelination, and behavioral abnormalities including autistic features.[2,3] Without appropriate treatment, CFD can lead to progressive and significant neurological dysfunction.

CFD most commonly results from impaired transport of folate across the choroid plexus into the central nervous system (CNS). Its causes can be genetic,[4] secondary to mitochondrial disorders,[5] or as a result of autoimmune mechanisms such as folate receptor alpha autoantibodies (FRAAs) that interfere with folate binding and transport.[6] The most clear-cut example of genetically-confirmed CFD is from mutations in the *FOLR1* gene, which encodes the folate receptor alpha, the main transporter of folate into the CNS.

Several emerging studies show that children with Autism Spectrum Disorder (ASD) frequently have abnormalities in their folate metabolism.[7,8] Likewise, several patients with confirmed CFD present with autism or autistic-like features.[9] This overlap between CFD and ASD is particularly important because ASD is typically regarded as a behavioral disorder with no approved medical treatments for its core symptoms. In some cases, identifying and addressing underlying abnormalities in folate metabolism may represent an important first step toward targeting the biological mechanisms of ASD.

About Wellcovorin

Wellcovorin is a formulation of leucovorin calcium tablets (5 mg and 25 mg) originally developed by GlaxoSmithKline (GSK) and approved for oncology-related indications, including use to mitigate the toxicity of folate antagonists such as methotrexate. Wellcovorin tablets were originally approved by the FDA in 1983. Due to the absence of patent protection and regulatory exclusivity, GSK discontinued manufacturing of the product in 1997. However, as the holder of the original New Drug Application (NDA), GSK retained regulatory authority to seek additional indications and update the product labeling.

Following a review of published literature and clinical case reports describing the use of leucovorin in a specific cohort of *FOLR1* patients with CFD, the FDA determined that leucovorin demonstrated meaningful therapeutic benefit for this patient population. In September 2025, the FDA requested that GSK update the NDA to include CFD as an additional approved indication.

In October 2025, GSK's Chief Executive Officer, Emma Walmsley, indicated that the company would comply with the FDA's request as an administrative update, but that GSK had no plans to pursue additional research, manufacturing, or commercial marketing of the product for CFD.[10]

Following GSK's recently approved updates, Wellcovorin's "Clinical Pharmacology" section now states:[11]

- Levoleucovorin has been observed to increase levels of 5-MTHF, an active metabolite of folate, in case studies of *FOLR1*-CFTD.
- Levoleucovorin and its metabolites (5,10-methenyltetrahydrofolate, 5,10-methylenetetrahydrofolate, and 5-MTHF) serve as cofactors in "one carbon" metabolism involved in the generation of nucleic acids and the regulation of gene expression.
- Leucovorin is a racemic mixture of (*l*)-or levoleucovorin and (*d*)-or dextroleucovorin.
- The apparent bioavailability of levoleucovorin is 97% for 25 mg, 75% for 50 mg, and 37% for 100 mg, and dextroleucovorin is approximately 19% for 25 mg, 20% for 50 mg, and 7% for 100 mg.

Implications of the FDA's Recent Decision

While GSK no longer manufactures Wellcovorin, it is the lead product on which several generic brands of leucovorin calcium tablets are based. Generic tablets for the U.S. population will soon be available for this new indication, based on Wellcovorin's updates.

Significantly, the FDA and GSK focused their review and eventual approval on the specific cases of Cerebral Folate Transport Deficiency (CFTD) caused by *FOLR1* mutations. Some media outlets have been critical of the FDA, stating that these recessive mutations are exceedingly rare with approximately 50 documented cases to date in literature.[12] This is true, and most children with genetically confirmed CFD are already taking leucovorin off-label, so this change may have little impact on the treatment of patients with this condition. However, our view on the FDA's action is quite different: we see this as a meaningful first step in expanding leucovorin's use for CFD and related neurological conditions.

Because patients with CFD represent a highly heterogeneous population, the FDA's focus on patients with *FOLR1*-related disease reflects a strategic, science-based, and practical approach. Patients with *FOLR1* mutations constitute a well-defined cohort with the clearest mechanistic link to CFD and the most robust clinical data, including EEGs, MRIs, and ongoing laboratory monitoring of folate levels in cerebrospinal fluid. They also represent patients with some of the highest dosing requirements for leucovorin. Many of these patients have been monitored over extended periods of time.

We appreciate that this action opens the door for using leucovorin to treat other forms of CFD, in which there are larger patient populations. Studies have shown that approximately 38% of children with Autism Spectrum Disorder

(ASD) have a form of CFD,[13] which means that the FDA's recent action may eventually translate into the treatment of ASD.

Future Needs and Development

While this step is a victory, it is not by any means the final destination. There is future work that must still be done.

Specifically, the folate molecules used in Wellcovorin and generic leucovorin calcium tablets are stereoisomers, meaning they are molecules that come in different 3D orientations (similar to how the left and right hands are mirror images of one another). As stated in Wellcovorin's clinical pharmacology section, leucovorin calcium is a racemic mixture, meaning that it contains equal parts of the active levo-isomer (*l*-isomer) and inactive dextro-isomer (*d*-isomer).

It is known that orally administer inactive isomer reaches the bloodstream, but because it is not metabolized and is excreted slowly, it persists in the blood for long periods of time with uncertain effects on folate transport and metabolic pathways.[14]

In the decades since the original approval of Wellcovorin, much of the pharmaceutical knowledge and landscape has changed. In 1992, the FDA, along with several other international bodies that oversee pharmaceutical manufacturing, enacted guidelines for developing drugs that have stereoisomeric composition. Their guidance states that *"geometric isomers and diastereoisomers therefore should, with the rare exception of cases where in vivo interconversion occurs, be treated as separate drugs and developed accordingly."*[15]

As an older racemic drug product originally developed for a different oncologic therapeutic indication before these guidelines were published, leucovorin calcium tablets represent an available but suboptimal treatment option for patients with CFD. These patients should receive only the bioactive, pure *l*-isomer.

As advances in genetics, metabolic medicine, immunology, and neurology have expanded our understanding of conditions associated with CFD, including complex neurodevelopmental disorders such as ASD, important limitations of legacy leucovorin formulations have become increasingly apparent. In particular, these older products were not designed to address the dosing flexibility, pharmacokinetic considerations, and patient-specific treatment needs that characterize modern management of CFD.

Several important limitations of existing leucovorin tablet formulations include the following:

1. **Formulations** – As previously mentioned, racemic leucovorin is currently available as a generic drug, and each brand uses different inactive ingredients such as milk derivatives, binders, and artificial dyes. These variations are often poorly tolerated by children with ASD and metabolic disorders. Incompatibility with GI sensitivities can lead to diarrhea, refusal to take medication, and reduced effectiveness and/or behavioral side effects. This adds to the heavy burden of caregiving for these patients.

2. **Inactive isomer**: Although leucovorin in lower doses for shorter periods has been found to be safe, the inactive portion of the drug, the *d*-isomer, can accumulate since it is not eliminated as quickly as the active portion of the drug. (The active isomer is very safe, and is quickly metabolized and eliminated.) Not much is known about the exact cause or effect of the consequences of the buildup of the inactive isomer. Children with CFD are commonly prescribed high doses for long periods of time and could have considerable build up. In similar situations, for the last few decades, the FDA has required single-isomer rather than racemic drugs.

3. **Shortages** – Generic leucovorin brands are prone to shortages, which may force families to switch products or interrupt treatment. Such disruptions, especially sudden discontinuation, can cause adverse side effects and possible regression in children who rely on consistent dosing.

4. **Substitution** – Because leucovorin is generic, a pharmacist can switch brands of leucovorin without notifying the family. As some brands are better tolerated than others, this can lead to sudden regression or behavioral problems which are typically unexplainable to the family.

5. **Uptake** – Many patients with CFD and ASD cannot tolerate current tablet formulations. Dysphagia (difficulty swallowing) is a frequently reported CFD symptom. In ASD patients, Avoidant/Restrictive Food Intake Disorder (ARFID) is common and further complicates medication acceptance and adherence. For many reasons, patients in this population (particularly young children) cannot safely swallow tablets. Compounded versions can reduce additives, but the taste and texture of these formulations are also barriers for uptake.

6. **Access** – Because leucovorin is currently used "off-label" for CFD and related conditions, many patients have trouble getting prescriptions and/or insurance coverage for leucovorin. This severely limits access to this treatment for patients who may benefit.

7. **Over-the-Counter (OTC) Supplements** – Because of some of the above issues, many patients turn to OTC folinic acid supplements since folinic acid is the active ingredient in leucovorin. We caution caregivers against this approach. Unlike FDA-approved medications, OTC supplements are not subject to rigorous monitoring or regulation. They often contain additional ingredients that may vary in quality and consistency. Another important concern is dosage. Most OTC folinic acid products are measured in micrograms (mcg), while leucovorin is prescribed in milligrams (mg). For reference, 1 mg equals 1,000 mcg: dosages that are too low are unlikely to be therapeutic. Additionally, it is critical not to confuse **folinic acid** with **folic acid**. Folic acid is a synthetic form of folate that is often sold as a supplement. **Folic acid** is metabolized differently than leucovorin and should not be used as a treatment for CFD or ASD.

The Approval of Leucovorin Validated Eletala's Development Goals

Eletala Enterprises Incorporated was born out of a need to serve a population of patients who are often missed by currently available testing, prevention, and drug treatment development projects. Founded by committed ASD and CFD specialists, we are dedicated to advancing therapeutics to support these patients and their families.

Specifically, for leucovorin, we are optimizing the formulation by removing the inactive isomer while also improving delivery mechanisms and tolerability for patients with unique needs. Our formulation can be mixed with water undetected – it is colorless, tasteless, and textureless – and was designed to improve compliance so that more children could have meaningful benefits from this life-altering treatment.

Importantly, we are developing products consistent with current FDA requirements for single-isomer drugs that eliminate unnecessary exposure to the inactive isomer. This also means that our products should allow the same therapeutic activity with half the dose.

In closing, we applaud the FDA's common sense approach to approving drugs for rare diseases, like CFD. While the actions announced this week are a major step-forward, leucovorin products still require improvement to resolve the critical issues surrounding the treatment availability, drug product variability, and impracticality of dosing racemic leucovorin tablets for this population. We believe that our efforts and the FDA's meaningful actions will be a major contribution to the care of children with CFD and eventually provide a pathway for better treatments for the underserved autism community.

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