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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2025-N-3959]

Approval of Previously Withdrawn New Drug Application for WELLCOVORIN (leucovorin calcium) Tablets

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing approval of the previously withdrawn new drug application (NDA) for Wellcovorin (leucovorin calcium) tablets, equivalent to (EQ) 5 milligrams (mg) base and EQ 25 mg base. FDA is initiating this action on the basis of new data and is required to publish notice of approval of an NDA for which the Agency had previously withdrawn approval.

FOR FURTHER INFORMATION CONTACT: Harold Sano, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 4355, Silver Spring, MD 20993-0002, 301-796-2429, Harold.Sano@fda.hhs.gov.

SUPPLEMENTARY INFORMATION: FDA is announcing approval of the previously withdrawn NDA 018342 for Wellcovorin (leucovorin calcium) tablets, EQ 5 mg base and EQ 25 mg base in accordance with 21 CFR 314.160, which provides, in relevant part, that FDA may, on the basis of new data, approve an application for which it had previously withdrawn approval.

Wellcovorin (leucovorin calcium) tablets, EQ 5 mg base and EQ 25 mg base, are the subject of NDA 018342, initially approved on July 8, 1983, and held by GlaxoSmithKline (GSK). The most recently approved labeling for Wellcovorin (leucovorin calcium) tablets, EQ 5 mg base and EQ 25 mg base, stated that the drug products were indicated to diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosages

of folic acid antagonists. In the Federal Register of September 22, 1999, FDA announced that it was withdrawing approval of NDA 018342 after GSK notified the Agency that Wellcovorin (leucovorin calcium) tablets, EQ 5 mg base and EQ 25 mg base, were no longer marketed and requested that the approval of the application be withdrawn under 21 CFR 314.150(c). Subsequently, in the Federal Register of April 28, 2017, FDA announced its determination that Wellcovorin (leucovorin calcium) tablets, EQ 5 mg base and EQ 25 mg base, were not withdrawn from sale for reasons of safety or effectiveness under 21 CFR 314.161.

Under 21 CFR 314.160, FDA, on its own initiative or upon request of an applicant, may, on the basis of new data, approve an application or abbreviated application which it had previously refused, suspended, or withdrawn approval. With respect to leucovorin calcium tablets, FDA has conducted a systematic analysis of literature published between 2009-2024 and has determined that the information supports a finding that orally administered leucovorin calcium tablets improve certain symptoms in adults and pediatric patients with cerebral folate deficiency (CFD). Published case reports provided patient-level data on over 40 patients, including both adults and pediatric patients, with genetically confirmed CFD due to variants in the FOLR1 gene who were treated with oral leucovorin. Patients had heterogenous clinical symptoms that included global developmental delays with autistic features and psychomotor regression, intractable epilepsy, and cerebellar ataxia. In some patients, leucovorin dosing was titrated based on levels of 5-methyltetrahydrofolate (5-MTHF) in the cerebrospinal fluid (CSF) or symptoms. Clinical outcomes were compared to the known natural history of CFD due to variants in the FOLR1 gene as historic control. The majority of patients demonstrated substantial improvement of symptoms of CFD that would not be expected when compared to the natural history of CFD due to FOLR1 gene variants. In addition, we reviewed mechanistic data that demonstrated a normalization in CSF 5-MTHF levels in 80% of patients who had CSF samples available for analysis following administration of leucovorin. We note that CFD has been reported in patients with neuropsychiatric symptoms, including autistic features, and detectable

serum autoantibodies to the folate receptor alpha; however, data on the use of leucovorin is limited in this population and additional studies are needed.

Subsequent to the approval of NDA 018342 for Wellcovorin (leucovorin calcium) tablets, EQ 5 mg base and EQ 25 mg base, that is being announced in this Notice, FDA intends to request that GSK submit a prior approval supplemental NDA to revise the prescribing information for Wellcovorin (leucovorin calcium) tablets, EQ 5 mg base and EQ 25 mg base, to include the essential scientific information needed for the safe and effective use of these drug products for the treatment of CFD in adults and pediatric patients.

Grace R. Graham,

Deputy Commissioner for Policy, Legislation, and International Affairs.

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