CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216395Orig1s000

SUMMARY REVIEW

Cross-Disciplinary Team Leader Memo

Application Type	505(b)(2)
Application Number(s)	NDA 216395
Priority or Standard	Standard
Submit Date(s)	03/26/2025
PDUFA Goal Date	PDUFA Goal Date 1/26/2026
Division/Office	Division of Nonmalignant Hematology (DNH)
Review Completion Date	See Stamp Date
Brand Name	Quiofic
Generic Name	Folic Acid
Pharmacologic Class	Vitamin B Complex
Applicant	CMP Development LLC
Applicant proposed Dosage form	Oral solution, 1 mg/5 mL
Applicant Proposed Indication(s)/Population(s)	QUIOFIC is effective in the treatment of megaloblastic anemias due to a deficiency of folic acid (as may be seen in tropical or nontropical sprue) and in anemias of nutritional origin, pregnancy, infancy, or childhood
Applicant proposed Dosing Regimen	• Therapeutic dosage in adults and children (regardless of age) is up to 1 mg (5 mL) daily. • Maintenance dosage - Infants: 0.1 mg (0.5 mL) daily - Children < 4 years: up to 0.3 mg (1.5 mL) daily - Adults and Children 4 years and older: 0.4 mg (2 mL) daily - Pregnant and Lactating Women: 0.8 mg (4 mL) daily; but never less than 0.1 mg (0.5 mL) per day
Recommendation on Regulatory Action	Approve
Recommended Dosage form	Oral Solution: 0.2 mg/mL
Recommended Indication(s)/Population(s)	Quiofic is indicated for the treatment of megaloblastic anemias due to folic acid deficiency in adult and pediatric patients.
Recommended Dosing Regimen	*Initial Dosing* The recommended starting dosage of QUIOFIC in pediatric and adult patients is up to 1 mg orally daily. QUIOFIC can be taken with or without food. Rule out pernicious anemia prior to use of any doses greater than 0.4 mg (except during pregnancy and lactation). *Maintenance Dosing* When clinical symptoms have subsided and the blood picture has become normal, use a daily maintenance level as follows: - Pediatric patients aged birth to 23 months: 0.1 mg orally daily

	- Pediatric patients aged 2 years to less than 4 years: up to 0.3 mg orally daily - Pediatric patients aged 4 years and older and adult patients: 0.4 mg orally daily - Pregnant and Lactating Women: 0.8 mg orally daily; but never less than 0.1 mg orally per day Higher maintenance doses may be needed in the presence of alcoholism, hemolytic anemia, anticonvulsant therapy, or chronic infection. Monitor patients frequently for relapse and adjust dose accordingly.

Reviewers of Multi-Disciplinary Review and Evaluation

Discipline/Office	Primary Reviewer/Secondary Reviewer
Office of Clinical Pharmacology	Ritika Kurian/ Sudharshan Hariharan
Clinical Reviewer	Patricia Oneal/ Margaret Thompson
Cross-Disciplinary Team Leader	Margaret Thompson
Division Labeling	Virginia Kwitkowski
Division Director (Signatory)	Tanya Wroblewski

Additional Reviewers of Application

OPDP	Melissa Khashei/ Jina Kwak
DPMH	Kevin Clark/ Tamara Johnson
OSE/DMEPA	Sue Black/ Nicole Iverson

OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

Glossary

BA	bioavailability
BE	bioequivalence
CMC	Chemistry, Manufacturing, and Controls
FDA	Food and Drug Administration
IND	investigational New Drug
iPSP	Initial Pediatric Study Plan
NDA	new drug application
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act

1 Division Director Division of NonMalignant Hematology (Signatory) Comment

I concur with the assessments of the clinical pharmacology and clinical review teams and agree with approval of Quiofic for the treatment of megaloblastic anemia due to deficiency of folic acid.

2 CDTL Summary Memo

Introduction: On March 26, 2026, the Applicant, CMP Development LLC , submitted a new drug application (NDA) for Quiofic (folic acid) oral solution, 1 mg/5 mL under the 505(b)(2) pathway. The Applicant is requesting approval only for the single indication for which the listed drug (LD), Folvite (folic acid 1 mg tablets, NDA # 005897) is approved, which is for "the treatment of megaloblastic anemias due to a deficiency of folic acid (as may be seen in tropical or nontropical sprue) and in anemias of nutritional origin, pregnancy, infancy, or childhood." The active moiety in Quiofic is folic acid (vitamin B9), the same as the active moiety of the LD. Quiofic differs from the LD only in dosage form.

Mechanism of action: Folic acid is a precursor of tetrahydrofolic acid, which is a cofactor involved in the biosynthesis of purine and thymidylates of nucleic acids. Impairment of thymidylate synthesis in patients with folic acid deficiency is thought to account for the defective DNA synthesis that leads to megaloblast formation and megaloblastic and macrocytic anemias. Thus, folic acid acts on megaloblastic bone marrow to produce a normoblastic marrow.

Demonstration of Safety and Effectiveness: The safety and effectiveness of Quiofic relies on FDA's previous assessment of the LD. Because the LD has been withdrawn from the market (see Regulatory History below), the Applicant used the Folic Acid Tablets 1 mg commercially available product (Amneal Pharmaceuticals LLC [ANDA #40625]) as the reference standard (RS) to establish a bridge between CMP's proposed drug product (folic acid oral solution 1 mg/5mL) and the LD, to support the scientific appropriateness of reliance on the LD through a comparative bioavailability/bioequivalence (BA/BE) study.

The clinical pharmacology of folic acid is well described in LD and the RS product labels and in published literature allowing CMP to support the NDA based upon a pharmacokinetic bridge with the RS. The Applicant submitted results from two clinical pharmacology studies, Study 007-24 and Study 008-24, to support the bridge from the RS to Quiofic. Review by the clinical pharmacology review division concluded the results of the bioequivalence studies conducted in this NDA submission establishes an adequate scientific bridge to Folvite and supports the approval of folic acid oral solution for the proposed indications at the doses approved for Folvite.

Benefit-Risk Assessment: The overall benefit-risk assessment of Quiofic for the treatment of megaloblastic anemias due to a deficiency of folic acid relies on the assessment of the LD. A literature review for new safety information regarding folic acid was conducted to determine whether the current labeling was sufficient to provide adequate instructions for use. There was no evidence of any new safety findings regarding folic acid not already included in the current USPI for approved folic acid products.

The BA/BE studies found that under fasting conditions, the exposure of folic acid from the test oral solution product was greater than that of the reference folic acid tablets. This was not observed in the fed state. The increased exposure observed in the fasted state is not expected to be clinically significant due to the wide safety margin of folic acid. This is because excess folic acid not used by the body is typically excreted in urine and folic acid has a short half-life. Therefore, the higher exposures will not lead to accumulation of folic acid upon repeat administration. Moreover, folic acid has been used in doses greater than the proposed dose of 1 mg with no serious safety concerns being reported. The safety of doses higher than the proposed dose was confirmed by a literature review. Thus, the benefit-risk assessment of folic acid for the treatment of megaloblastic anemia associated with folic acid deficiency in adult and pediatric patients remains favorable.

Conclusions and Recommendation
The Applicant submitted a 505(b)(2) application for Quiofic (folic acid) oral solution, relying on non-clinical, efficacy, and safety assessments of the LD previously reviewed as part of the approval of the LD in the requested indication. The applicant submitted clinical data from two studies in healthy volunteers establishing bioequivalence between their product and the RS.

Based on the favorable benefit-risk assessments of the LD for the requested indication, established as part of the Agency's approvals for the LD, which has remained unchanged in the post market setting, along with the establishment of bioequivalence between the RS and the Applicant's product, the Division recommends approval of Quiofic (folic acid solution 0.2 mg/mL) for the treatment of megaloblastic anemias due to folic acid deficiency in adult and pediatric patients.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Folvite, the LD, was first approved in 1947 under NDA 005897. In 2016, the Application holder requested withdrawal of their product. It is currently listed in the Orange Book as Discontinued-not for safety or efficacy reasons.

The reference standard (RS) is the folic acid tablet, 1 mg, supplied Amneal Pharmaceuticals and was approved July 2005 (ANDA 040625).

3.2. Summary of Presubmission/Submission Regulatory Activity

A type B PIND 144328 written response only meeting was held between the Applicant and FDA, with responses provided October 27, 2022. Key advice included:

- Agreement with plan to prioritize enrollment of individuals with low to no production of endogenous substances instead of ensuring enrollment of equal numbers of male and female subjects.
- Agreement with 72-hour washout period from the first dose of administration.
- We did not agree with establishing BE on (b) (4) Therefore, bioequivalence should be established based on parental drug (active ingredient), i.e., folic acid, because exposure of the parent drug is more sensitive to changes in drug formulation.

4 Summary of Review Disciplines

4.1. Office of Scientific Investigations (OSI)

The Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not needed for this application because they had conducted a Remote Regulatory Assessment (RRA) for the site where the BE/BC studies[1] were conducted in (b) (4) for a different application (ANDA (b) (4)). OSIS concluded that data from the reviewed study was reliable.

4.2. Product Quality

The Office of Pharmaceutical Quality (OPQ) recommends approval from all OPQ disciplines. This is based on the following:

- The applicant of this 505(b)(2) NDA has provided sufficient Chemistry, Manufacturing, and Controls (CMC) information to ensure the identity, strength, purity, and quality of the drug product QUIOFIC (folic acid) oral solution, 1 mg / 5 mL (0.2 mg/mL).
- The Office of Pharmaceutical Manufacturing Assessment (OPMA) has made the overall manufacturing inspection recommendation of "Approve" for the facilities involved in this application.
- The CMC recommended changes to the labeling have been communicated to the applicant through the Clinical Review Team, and the recommended CMC revisions have been accepted.
- The applicant's request for categorical exclusion from the preparation of an environmental assessment has been found adequate and is granted.

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[1] (b) (4)

For additional details, see Integrated Quality Review uploaded to DARRTS December 10, 2025.

4.3. Clinical Microbiology

Not Applicable

4.4. Devices and Companion Diagnostic Issues

Not Applicable

5 Nonclinical Pharmacology/Toxicology

The Applicant relied on non-clinical pharmacology/toxicology from the LD and no nonclinical information was submitted with the application.

6 Clinical Pharmacology

The Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology (OCP/DCEP reviewed pharmacokinetic (PK) data submitted with the application, derived from the two relative BA/BE Studies and recommends approval. The results of the bioequivalence studies conducted in this NDA submission establishes an adequate scientific bridge to Folvite and supports the approval of folic acid oral solution for the proposed indications at the doses approved for Folvite.

- The results of the bioequivalence study 007-24 demonstrated that folic acid 1 mg/5ml oral solution under fasting conditions resulted in a relatively higher exposure of folic acid compared to the reference product. However, the higher bioavailability of folic acid under fasting conditions is not clinically significant.
- The results of the bioequivalence study 008-24 demonstrated that folic acid exposure between the 1 mg/5ml oral solution and the reference product under fed conditions is comparable. The marginally lower Cmax of folic acid from the test product is not clinically significant.

For additional details, see Office of Clinical Pharmacology Review uploaded to DARRTS January 16, 2026.

7 Clinical

The Applicant is relying on FDA's assessments of the safety and efficacy of the LD. No efficacy data is included with the submission. Clinical conducted a literature review to identify any newly identified safety issues for folic acid not already included in the United States Prescribing Information (USPI) for the LD and to evaluate the potential risk of higher exposure observed with Quiofic in the fed state. No new safety issues were identified. Clinical recommends approval.

For additional details see Clinical review uploaded to DARRTS 1/26/2026.

8 Pediatrics

The Applicant included in the submission their agreed upon initial pediatric study plan (iPSP), which stated "a pediatric assessment is satisfied by demonstration of bioequivalence to the reference standard (folic acid oral tablets) which is adequately labeled for all pediatric age groups." The Applicant has fulfilled PREA requirements.

9 Labeling Recommendations

The Applicant submitted draft labeling with their NDA application which was consistent with the USPI for the LD. FDA negotiated changes to the USPI based on current standards. These revisions included a change in the indication language to:

- Quiofic is indicated for the treatment of megaloblastic anemias due to folic acid deficiency in adult and pediatric patients.

For full details, see primary labeling review uploaded to DARRTS January 6, 2026.

10 Postmarketing Requirements and Commitment

None

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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01/26/2026 03:16:40 PM

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