

Folafy[®] ER

((6S)-5-methyltetrahydrofolic acid, glucosamine salt)
For adjunctive use with antidepressant therapy

Folafy[®] ER is an orally administered medical food* for use only under the supervision of a physician for the metabolic management of low 5-methyltetrahydrofolic acid (5-MTHF) levels associated with depression.



Discussion

Folafy ER provides a proprietary biologically active folate, 5-MTHF glucosamine salt, also known as Quatrefolic[®]. Research suggests that the involvement of folate (specifically 5-MTHF) in neurotransmitter synthesis is primarily responsible for its effects on mood and cognition. Folate, in the form of 5-MTHF, bypasses the need for folate to be converted to its active form and overcomes the challenge of improving folate status in individuals with certain genetic polymorphisms.^[1]

5-MTHF is the active, circulating form of folate and the main form found naturally in food. Unlike supplementary folic acid, which requires enzymatic conversion to become biologically active, 5-MTHF is able to penetrate cellular membranes without being metabolized.

MTHFR Polymorphism

Methylenetetrahydrofolate reductase (MTHFR) is an enzyme necessary for the conversion of folate to 5-MTHF. There is a significant association between MTHFR polymorphism and depression risk.^[2] 5-MTHF plays a key role in the manufacture of S-adenosylmethionine (SAMe); methylation of DNA, proteins, neurotransmitters, and phospholipids; and remethylation of homocysteine to methionine.^[1,3,4] Nutrigenomic research indicates that some individuals, due to their unique genetic patterns and expression, do not produce adequate or effective MTHFR.^[1,5]

Research has shown racemic 5-MTHF to be seven times more bioavailable than folic acid.^[6] In other research, 5-MTHF was more effective than folic acid at increasing total plasma folate concentrations in subjects with the TT and CC genotype of the 677C→T mutation of MTHFR.^[7]

Quatrefolic

Quatrefolic is a new dietary ingredient (NDI) that shows enhanced stability and bioavailability when compared to the calcium salt form of 5-MTHF. In a direct comparison

between Quatrefolic, (6S)-5-methyltetrahydrofolate calcium salt, and folic acid in rats, Quatrefolic demonstrated a much higher absorption rate within the first two hours (1918.8, 1061.9, and 614.0 nmol/l plasma, respectively).^[8] In a single-dose, balanced, two-sequence, two-period, two-treatment, randomized, crossover human study, Quatrefolic showed better bioavailability (+10%) than (6S)-5-MTHF calcium salt (Ca-L-5-MTHF).^[9]

5-MTHF and Depression

According to some researchers, depression is very common. In fact, it is estimated that one-fourth of the US population will have a depressive episode sometime in their lives.^[1] 5-MTHF is involved in the metabolic management of low 5-MTHF levels associated with depression by supporting the body's ability to regulate the biosynthesis of brain neurotransmitters, such as serotonin, norepinephrine, and dopamine.^[1,10] For instance, 5-MTHF participates in the remethylation of homocysteine to create methionine. Furthermore, SAMe is the downstream metabolite of methionine, but it needs 5-MTHF to be manufactured. SAMe is believed to be involved in numerous biochemical methyl donation reactions, including reactions forming monoamine neurotransmitters.^[1] Researchers believe that inadequate 5-MTHF, as a consequence of folate deficiency or from the inability to sufficiently convert folic acid to 5-MTHF, impacts the complex balance of brain neurotransmitters.^[1,11,12] Supplementation with oral 5-MTHF has proven beneficial in depressive disorders.^[11,13]

Adjunctive Use of 5-MTHF in Major Depressive Disorder

Folafy ER is indicated for the distinct nutritional requirements of individuals who have suboptimal 5-MTHF in their cerebrospinal fluid, plasma, and/or red blood cells. It is also indicated for those who have major depressive disorder (MDD), with particular emphasis as adjunctive support for individuals who are on an antidepressant. Folafy ER is indicated regardless of MTHFR C677T polymorphism genotype.

It is important to note that folic acid, when administered in daily doses above 0.1 mg, may obscure the detection of B12 deficiency.

See page two of the Fofafy ER Product Detail Sheet for additional information on the clinical pharmacology, contraindications, precautions, patient information, and interaction with drugs for Fofafy ER.

USP (United States Pharmacopeia) Dissolution Rate, USP-Grade Excipients

To support excellent quality and provide for the extended release of Quatrefofic, Fofafy ER has been designed to meet the criteria for rate of dissolution and disintegration according to USP 711 Dissolution, Method A for delayed-release dosage forms. In addition, the natural-source excipients used in Fofafy ER are USP grade, meaning they meet all of the specifications the USP establishes in their monograph for each ingredient.

*Medical foods are "intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation" (section 5(b)(3) of the Orphan Drug Act (21 U.S.C. 360ee(b)(3)). Such patients may have a limited or impaired capacity to ingest, digest, absorb, or metabolize ordinary foodstuffs or certain nutrients, or have other special medically determined nutrient requirements that cannot be achieved by modification of the normal diet alone.

Fofafy® ER

INGREDIENTS: Dicalcium phosphate dihydrate, microcrystalline cellulose, coating (talc, shellac, vegetable glycerin, L-arginine, vegetable magnesium stearate, silica, sodium alginate, titanium dioxide, riboflavin 5'-phosphate sodium), vegetable stearic acid, (6S)-5-methyltetrahydrofolic acid glucosamine salt,^{S1} vegetable magnesium stearate, and croscarmellose sodium.

DIRECTIONS: Take one tablet daily with or without food, or as directed by your physician.

STORAGE: Store at 20° to 25°C (68° to 77°F).

WARNING: For use under supervision of a physician. Keep this and all medications out of the reach of children.

Each tablet delivers:

Folate (as [6S]-5-methyltetrahydrofolic acid, glucosamine salt) ... 25,500 mcg DFE*

*Previously stated as 15 mg

 **Quatrefofic** ...S1. Quatrefofic® is a registered trademark of Gnosis S.p.A. Produced under U.S. Patent 7,947,662.

References

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Additional references available upon request