

XaQuil® XR

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

XaQuil® XR 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

XaQuil® XR provides Quatrefolic®, a patented glucosamine salt of (6S)-5-methyltetrahydrofolate. Quatrefolic is a proprietary and biologically active form of folate, also known as vitamin B9. Folic acid and dietary folate are converted by the methylenetetrahydrofolate reductase (MTHFR) enzyme to 5-methyltetrahydrofolate (5-MTHF), the biologically active form of folate in the body. Supplementation of folate in the form of Quatrefolic bypasses the need for conversion by the MTHFR enzyme as it delivers the 5-MTHF molecule in its biologically active form. This can help overcome the challenges of improving folate status in individuals with certain genetic polymorphisms.¹

MTHFR Polymorphism

The MTHFR enzyme is necessary for converting folic acid and dietary folate to 5-MTHF. The bioactive form of folate, 5-MTHF, plays a key role in the manufacture of S-adenosylmethionine (SAME); methylation of DNA, proteins, neurotransmitters, and phospholipids; and methylation of homocysteine to methionine.¹⁻⁴ Nutrigenomic research indicates that because of their unique genetic patterns and expression, some individuals do not produce adequate or effective MTHFR.^{1,5}

Research has shown Quatrefolic to be 7 times more bioavailable than folic acid.⁶ In other research, Quatrefolic 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 patented dietary ingredient that shows enhanced stability and bioavailability compared with the calcium salt form of L-5-methyltetrahydrofolate. In a direct comparison between Quatrefolic, L-5-methyltetrahydrofolate calcium salt, and folic acid in rats, Quatrefolic demonstrated a much higher absorption rate. The Quatrefolic arm demonstrated a plasma concentration peak 1.8× higher than L-5-methyltetrahydrofolate calcium salt and 3.1× higher

than folic acid.⁸ In a single-dose, balanced, 2-sequence, 2-period, 2-treatment, randomized, crossover human study, Quatrefolic showed better bioavailability (+10%) than L-5-methyltetrahydrofolate calcium salt.⁹

5-MTHF and Depression

It is estimated that one-fourth of the US population will have a depressive episode sometime in their lives.¹ There is a significant association between *MTHFR* polymorphism and depression risk.² 5-MTHF supports the biosynthesis of brain neurotransmitters like serotonin, norepinephrine, and dopamine.^{1,10} For example, 5-MTHF is required for the methylation of homocysteine to create methionine, and SAME is the downstream metabolite of methionine. Without enough 5-MTHF, SAME levels will decline. SAME is involved in many biochemical methyl donation reactions, including the formation of monoamine neurotransmitters.¹ Researchers believe that inadequate 5-MTHF, whether due to folate deficiency or the inability to sufficiently convert dietary folate and folic acid to 5-MTHF, impacts the complex balance of brain neurotransmitters.^{1,11,12} Supplementation with oral 5-MTHF has been reported as beneficial in depressive disorders.^{11,13}

Adjunctive Use of 5-MTHF in Major Depressive Disorder

Bioavailable forms of folate, like Quatrefolic in XaQuil XR, are 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 with major depressive disorder (MDD), with particular emphasis on adjunctive support for individuals who are on an antidepressant. Bioavailable forms of folate are indicated in MDD, regardless of the *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. The (6S)-5-methyltetrahydrofolic acid forms of folate, like Quatrefolic in XaQuil XR, do not mask B12 deficiency.

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

To support excellent quality and provide for the extended release of Quatrefolic, XaQuil XR has been designed to meet the criteria for the 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 XaQuil XR are USP grade, meaning they meet all of the specifications the USP establishes in their monograph for each ingredient.

Vegetarians

The glucosamine in Quatrefolic is animal and shellfish free and is an excellent option for vegetarians.

*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.

XaQuil® XR

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.

USUAL DOSAGE: 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

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

References

1. Miller AL. The methylation, neurotransmitter, and antioxidant connections between folate and depression. *Altern Med Rev*. 2008;13(3):216-226.
2. Rai V. Genetic polymorphisms of methylenetetrahydrofolate reductase (MTHFR) gene and susceptibility to depression in Asian population: a systematic meta-analysis. *Cell Mol Biol (Noisy-le-grand)*. 2014;60(3):29-36.
3. Scaglione F, Panzavolta G. Folate, folic acid and 5-methyltetrahydrofolate are not the same thing. *Xenobiotica*. 2014;44(5):480-488. doi:10.3109/00498254.2013.845705
4. Papakostas GI, Cassiello CF, Iovieno N. Folates and S-adenosylmethionine for major depressive disorder. *Can J Psychiatry*. 2012;57(7):406-413. doi:10.1177/070674371205700703
5. Bueno O, Molloy AM, Fernandez-Ballart JD, et al. Common polymorphisms that affect folate transport or metabolism modify the effect of the MTHFR 677C>T polymorphism on folate status. *J Nutr*. 2016;146(1):1-8. doi:10.3945/jn.115.223685
6. Willems FF, Boers GH, Blom HJ, et al. Pharmacokinetic study on the utilisation of 5-methyltetrahydrofolate and folic acid in patients with coronary artery disease. *Br J Pharmacol*. 2004;141(5):825-830. doi:10.1038/sj.bjp.0705446
7. Prinz-Langenohl R, Brämwig S, Tobolski O, et al. [6S]-5-methyltetrahydrofolate increases plasma folate more effectively than folic acid in women with the homozygous or wild-type 677C>T polymorphism of methylenetetrahydrofolate reductase. *Br J Pharmacol*. 2009;158(8):2014-2021. doi:10.1111/j.1476-5381.2009.00492.x
8. Miraglia N, Agostinetti M, Bianchi D, et al. Enhanced oral bioavailability of a novel folate salt: comparison with folic acid and a calcium folate salt in a pharmacokinetic study in rats. *Minerva Ginecol*. 2016;68(2):99-105.
9. Crossover comparative bioavailability study of 5-methyltetrahydrofolate glucosamine salt (GN10G) compared to the reference Metafolin® in healthy volunteers. IPAS-5MTHFA-583-09 final report. Desio, Italy: Gnosis by LeSaffre; March 15, 2010: 1-33. [available from the manufacturer Gnosis by LeSaffre upon request]
10. Fava M, Mischoulon D. Folate in depression: efficacy, safety, differences in formulations, and clinical issues. *J Clin Psychiatry*. 2009;70 Suppl 5:12-17. doi:10.4088/JCP.8157su1c.03
11. Godfrey PS, Toone BK, Carney MW, et al. Enhancement of recovery from psychiatric illness by methylfolate. *Lancet*. 1990;336(8712):392-395. doi:10.1016/0140-6736(90)91942-4
12. Peerbooms OL, van Os J, Drukker M, et al. Meta-analysis of MTHFR gene variants in schizophrenia, bipolar disorder and unipolar depressive disorder: evidence for a common genetic vulnerability? *Brain Behav Immun*. 2011;25(8):1530-1543. doi:10.1016/j.bbi.2010.12.006
13. Guaraldi GP, Fava M, Mazzi F, et al. An open trial of methyltetrahydrofolate in elderly depressed patients. *Ann Clin Psychiatry*. 1993;5(2):101-115. doi:10.3109/10401239309148970