Quatrefolic®

The innovACTIVE folate!

Gnosis by Lesaffre

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FOLIC ACID

Supplements/
Fortified Foods

DHFR

Absorption

UMFA

Folic acid supplementation may lead to a build-up of Unmetabolized Folic Acid (UMFA) in systemic circulation with potential toxic effects.

Quatrefolic®, the "active form" of folate does not promote the potential accumulation of UMFA in the blood.

DHF
dihydrofolate

DHFR

THF
tetrahydro-folate

DIETARY FOLATE
Leafy vegetable & Legumes

In Humans, gut has limited ability to reduce folic acid that reaches the liver in the non-active form.

There are big variations in how efficiently folic acid and folate are converted to the bioactive form in different people due to defect of MTHFR activity.

Quatrefolic® is mainly absorbed in the small intestine by a carrier mediated mechanism. The carrier is not saturated and this enables Quatrefolic® to ensure a higher folate uptake.

5,10
methylene-THF

Quatrefolic® completely bypasses the "damaged" MTHFR conversion step and delivers a "finished" folate the body can immediately use without any kind of metabolization.

MTHFR

MTHFR C-T Polymorphism

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5-MTHF
(L-Methylfolate active form)

(Ref. 1, 2, 3)

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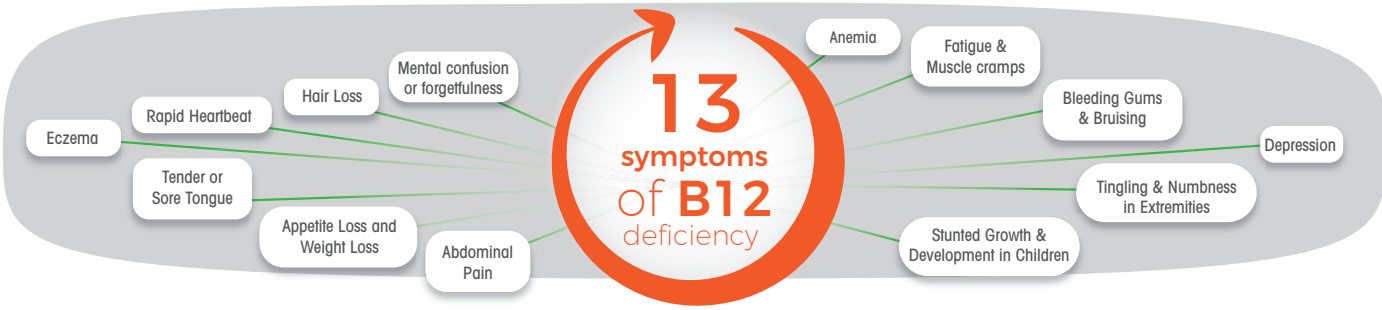
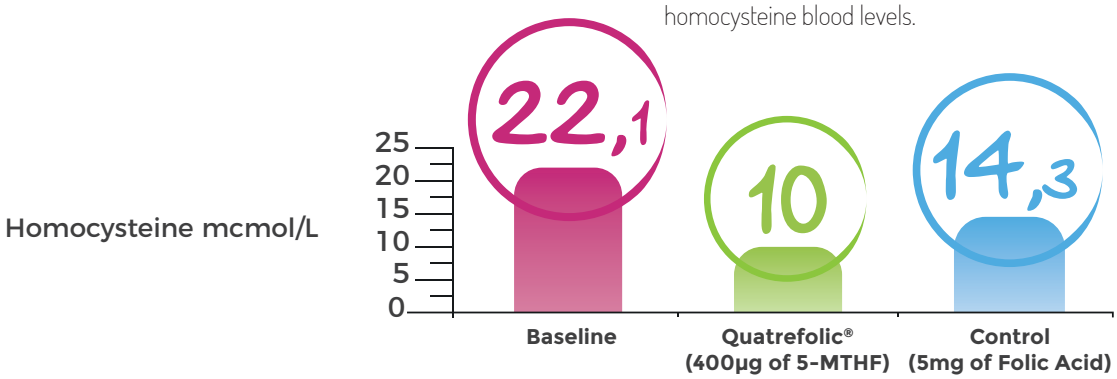
Folic acid	Quatrefolic®
Folic acid itself is not active and must be metabolized through several steps in order to enter the folate cycle.	Main folate form in blood and cord serum. It is the **biologically active form**. It can enter the folate cycle directly.
Unmetabolized folic acid is found in blood at doses >200 µg / day and may relate to potential adverse effects on human health. In the brain it can bound folate receptor blocking 5-MTHF adsorption.	**No unmetabolized** folic acid with **Quatrefolic®**, for a safe and full active folate efficacy. **Quatrefolic®** crosses Blood Brain Barrier.
Less bioavailability.	**Higher bioavailability:** Pre-clinical study in vivo with **Quatrefolic®** showed a plasmatic (6S)-5-MTHF concentration peak about **3 times higher** with **Quatrefolic®** than folic acid.
High doses of folic acid can mask vitamin B12 deficiency and delay its diagnosis by correcting hematological signs.	As **Quatrefolic®** is already the biologically active form, it doesn't mask the vitamin B12 deficiency.



Folic acid upper tolerable limit is 1mg /day.	**No upper tolerable limit of Quatrefolic®** in US dietary reference intakes. Safety of (6S)-5-MTHF has been confirmed by several studies.
5, 10-Methylenetetrahydrofolate reductase (MTHFR) enzyme polymorphism problem: In carriers of mutated homozygotes **677T->T** genotype the enzyme activity of the MTHFR is about **70% less than normal**, and heterozygotes **677C->T 30-40% less than normal**. The reduction in MTHFR activity **increases homocysteine levels and reduces the availability of the DNA methyl groups.**	**As Quatrefolic®** is already the biologically active form, **the problem of people with 677C->T or 677T->T polymorphisms in folate-related enzymes (especially MTHFR) doesn't exist anymore.**
Practically not soluble in water.	**Quatrefolic® is totally soluble in water.**
Lesser efficacy in lowering hyperhomocysteinemia.	**Quatrefolic®** it is more effective in lowering and normalizing altered homocysteine blood levels.



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2. Patanwala I et al. Folic acid handling by the human gut: implications for food fortification and supplementation. Am J Clin Nutr. 2014
3. Ulrich CM, Potter JD. Folate supplementation: too much of a good thing? Cancer Epidemiol Biomarkers Prev. 2006
4. Bailey LB et al. Folate metabolism and requirements. J Nutr. 1999
5. Mazza A. et al. Nutraceutical approaches to homocysteine lowering in hypertensive subjects at low cardiovascular risk: a multicenter, randomized clinical trial. Biol Regul Homeost Agents 2016

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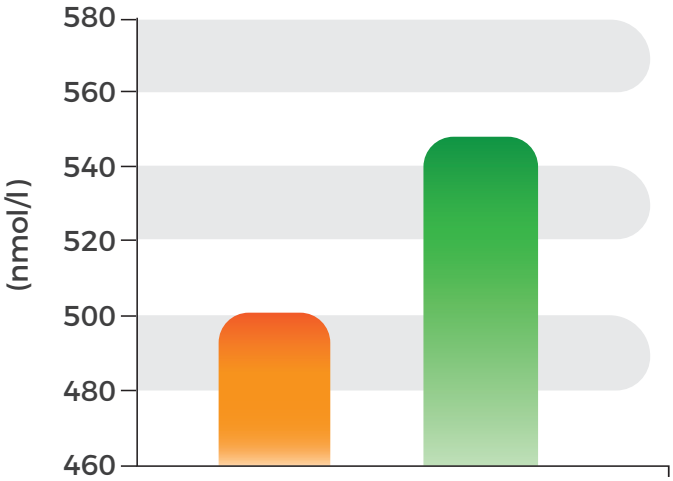
(6S)-5-MTHF Ca Salt	Quatrefolic®
(6S)-5-MTHF Ca Salt is stable only at temperature between 2-8°C.	**Quatrefolic®** is lyophilized and is stable at room temperature 25°C.
(6S)-5-MTHF Ca Salt is less bioavailable.	Higher bioavailability: Pre-clinical study in vivo with **Quatrefolic®** showed a plasmatic (6S)-5-MTHF concentration peak about 20% times higher with **Quatrefolic®** than (6S)-5-MTHF calcium salt.

Quatrefolic® and 5-methyltetrahydrofolate: pharmacokinetic comparison



PK parameters (AUC_{12h}) - (6S)-5-methyltetrahydrofolate Ca Salt vs. Quatrefolic (400µg dose) ● 5-methyltetrahydrofolate Ca Salt ● Quatrefolic®

The human clinical study confirms that **Quatrefolic®** owns a superior bioavailability profile over the (6S)-5-methyltetrahydrofolate calcium salt (Metafolin®) of about 10%.

100 times less soluble in water than **Quatrefolic®**.	**Quatrefolic®** is totally soluble in water.

Quatrefolic® is 100 times more soluble in water than calcium salt.

5-methyltetrahydrofolate calcium salt

Quatrefolic®

(6S)-5-MTHF Ca Salt is a crystalline salt.	**Quatrefolic®** is in **amorphous status,** offering **a higher solubility and good stability.** This guarantees an homogeneous and reproducible solubilization process compared with the crystalline alternative salt.
Solubilizing agents are often used to facilitate drying of calcium salt forms.	**No solubilizing agents** used to facilitate drying of **Quatrefolic®**.

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Quatrefolic®

The innovACTIVE folate for:

Human Well-being

Folate is a cofactor in many vital biological reactions and its deficiency may be present at all stages of life.

Quatrefolic® may sustain right cells functions and human body well-being.

Preconception, Pregnancy and Lactation

Studies have found that low dietary intake of folate increases the risk of birth defects.

Quatrefolic®, as a source of (6S)-5-methyltetrahydrofolate (5-MTHF), might be particularly useful to provide the nutritionally active form of folate during preconception, pregnancy and lactation.

Women and Men Infertility

Low circulating active folate affects unexplained female and men infertility, with MTHFR polymorphism and homocysteine status that can disturb the early stages of human reproduction.

Quatrefolic® supplementation can be an effective help in infertility, as demonstrated in a case series study in couples with recurrent miscarriages lasting for at least 4 years (+86.7%)

Infants and Children

Folate is a critical nutrient when human cells growth is very active and folate deficiency can slow overall growth rate.

In infants, children and adolescents Quatrefolic® could be recommended to prevent anemia, to sustain tissue growth, normal brain development and function, and red blood cells and energy production.

Mood and Brain Health

Folate is involved in the production of key neurotransmitters of the brain and its deficiency can affect the mood status.

Quatrefolic® supplementation may contribute to the relief of mood and support people with mood impairments and disorders.

Aging, Heart and Older people

The prevalence of folate deficiency in the older population is approximately 30%. High homocysteine levels are associated with cardiovascular problems and vascular brain impairment. Folate deficiency is also a recognized factor for cognitive decline and incident dementia.

At low dose, Quatrefolic® has shown to normalize homocysteine better than high dose of folic acid. Its supplementation may help to modulate brain and mental functions, reducing the development of brain decline.

Active Lifestyle and Sport

In people playing physical exercise as well as in athletes, folate has a direct role in the synthesis of new cells and in the building and repairing of body tissues, including those injured due to physical activity.

Quatrefolic® has a central role in red blood cells production and energy, supports the immune system, can help to normalize homocysteine levels and protects body structures controlling inflammation.

Quatrefolic®

The innovACTIVE folate!

- The biologically active form of folate, everyone can immediately utilize without any kind of metabolization
- The only form of folate crossing the blood-brain barrier
- High water solubility for improved bioavailability
- Supported by pre-clinical and clinical data
- Extensive Intellectual Property for production/purification processes (US 7,947,662 - EP 2245032 - EP 2254890 - PCT/EP2008/52034)
- Quatrefolic® has greater formulation flexibility in tablets, capsules, softgels, instant drinks and unconventional formulations such as granular and powdered microencapsulated forms

These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.
This is a business-to-business information intended for food and supplement producers, and is not intended for the final consumer.
Manufacturers should check local regulatory status of any claims according to the intended use of their products.

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