

OCUFOLIN PRODUCT INSERT

A safe, effective medical food specially formulated for the clinical dietary management of metabolic imbalances associated with retinal and choroidal ischemia and their related vascular eye disorders.

A medical food is an FDA regulated category of products intended for the dietary management of a disease or a condition that has distinct nutritional requirements associated with inborn errors of metabolism. The key ingredients used in medical foods for the indication must be Generally Recognized as Safe (GRAS). Medical foods may be associated with fewer side effects that are commonly seen with prescription or over-the-counter products. All key ingredients in Ocufofin are GRAS and have a long history of safe clinical use.

OCUFOLIN DESCRIPTION:

1. Indication

Ocufofin is a medical food indicated for the distinct nutritional requirements of individuals who have reduced innate capacity to metabolize synthetic folic acid and folate into its biologically-active form, L-methylfolate, resulting in an increased risk for vascular eye disorders. Ocufofin contains a proprietary formulation of vitamins, minerals, carotenoids, and glutathione precursors for the clinical dietary management of the metabolic imbalances underlying retinal and choroidal ischemia and their related vascular disorders. Ocufofin must be administered under medical supervision.

Retinal and Choroidal Ischemia as a Metabolic Deficiency

Ischemia is a broad term for chronic reduced blood flow, resulting in hypoxia, energy depletion, and cell death. Reduced blood flow in the retinal and the choroidal vessels can initiate or contribute to retinal vascular conditions such as macular degeneration, retinal microaneurisms, retinal vein or artery occlusions, and vascular retinopathies, producing symptoms such as blurred or distorted vision or loss of vision.

Retinal and choroidal ischemia may be caused by systemic vascular disorders such as hypertension and atherosclerosis. Hyperhomocysteinemia, a medical condition characterized by elevated levels of homocysteine in the blood has been identified as an independent risk factor for many systemic vascular conditions^{1,2,3,4} as well as common vascular conditions of the eye³ including retinal vein or artery occlusions,^{5,6,7,8,9,10,11,12,13,14} nonarteritic anterior ischemic optic neuropathy (NAION)¹⁴ and age-related macular degeneration (AMD).^{15,16,17,18,19,20}

Numerous human epidemiological studies have shown homocysteine levels correlate inversely and closely with plasma folate levels.⁴ In addition to poor diet and lifestyle factors, folate deficiencies may also result from malabsorption of dietary folates, as in the case of Celiac,²¹ Crohn's,²² bariatric surgery,²³ and alcoholism.²⁴ Inborn genetic defects²⁵ and medications may also cause interference with normal folate uptake and metabolism, ultimately reducing the availability of biologically-active L-methylfolate. Among such medications are dihydrofolate reductase inhibitors, sulfonamides, oral contraceptives, anticonvulsants,^{4,26} metformin,²⁷ fluoxetine,²⁸ levodopa,²⁹ warfarin,³⁰ proton pump inhibitors,³¹ and H2 antagonists.³¹ Intake of synthetic folic acid itself, if

greater than 400 mcg daily, may also fail to be metabolized and act as a competitive inhibitor of transport of L-methylfolate.³² These same factors that affect intracellular folate uptake and metabolism are also risk factors for hyperhomocysteinemia.⁴

The most common genetic causes of hyperhomocysteinemia are inborn genetic variations (polymorphisms) in the Methyltetrahydrofolate Reductase (MTHFR) gene.⁴ The MTHFR gene produces the MTHFR enzyme that catalyzes the metabolic conversion of dietary folic acid to its bioactive form, L-methylfolate. L-methylfolate is used by the body in many biochemical pathways, most importantly in the recycling of homocysteine back into methionine. It is estimated that homozygous and compound heterozygous MTHFR genotypes are present in more than 30% of the US population³³ and therefore may have associated impaired vascular health. Specifically, research has shown that there are direct associations between polymorphisms in the MTHFR gene and elevated levels of homocysteine.^{34,35,36,37} The resulting systemic vascular conditions^{38,39,40,41,42} and many vascular disorders of the eye include:

- Retinal vein or artery occlusions^{43,44,45,46,47,48,49,50}
- Retinopathy^{51,52,53,54,55,56,57,}
- Age-related macular degeneration (AMD)^{58,59,60}
- Non-arteritic anterior ischemic optic neuropathy (NAION)⁶¹

Elevated plasma levels of homocysteine have also been associated with increased oxidative stress, as measured by total antioxidant capacity.⁶² Homocysteine's effect on oxidative stress is possibly due to decreased expression and/or activity of key antioxidant enzymes, as well as increased generation of damaging reactive oxygen species (ROS).⁶³ Homocysteine specifically has been shown to promote oxidant injury to the vascular endothelium⁶⁴ and subsequent endothelial dysfunction, the major pathophysiologic mechanism that causes vascular disorders.^{4,65} Evidence of increased oxidative stress and elevated homocysteine have been correlated with depleted levels of the endogenous antioxidant glutathione in patients with vascular eye disorders.^{66,67,68}

Mechanism of Action

Ocufolin acts by optimizing intracellular antioxidants, vitamins, and N-Acetylcysteine levels so that impaired folate methylation is improved, restoring efficiency of the conversion of homocysteine into methionine, and reducing oxidative stress by increasing intracellular glutathione. Lower homocysteine levels and improved glutathione levels improve vascular health and are neuroprotective against the continuous high level oxidative metabolic stress experienced by the retina in general, and the macula in particular.

2. Ingredients

Ocufolin is a medical food containing a proprietary blend of key vitamins, minerals, and carotenoids to help manage homocysteine levels resulting from metabolic active folate deficiencies caused by certain medical conditions, MTHFR polymorphisms, and medications. Ocufolin was also formulated to help protect retinal, choroidal and macular tissue from oxidative stress caused by high levels of homocysteine.

Key Ingredients

Metafolin® [(6S)-5-methyltetrahydrofolic acid, calcium salt (L-Methylfolate)]

Individuals with some chronic illnesses, on certain medications, or with genetic MTHFR deficiencies, cannot efficiently metabolize dietary folate or folic acid into the bioactive form of folate, L-methylfolate, which is required for reducing homocysteine levels. Therefore, supplementation with L-methylfolate may be beneficial. Clinical studies have concluded that direct supplementation with L-methylfolate reduces homocysteine levels more effectively than folic acid.^{69,70} In fact, folic acid supplementation alone was shown not to reduce intracellular homocysteine.⁷¹ L-methylfolate was especially effective in individuals with MTHFR genetic variations, as it was shown to lower homocysteine levels and improve plasma folate.^{72,73}

B-Vitamins

Vitamins B6 and B12 status has been associated with elevated homocysteine.^{4,74,75,76} In conjunction with supplemented folate, the addition of Vitamin B12 has been shown to reduce homocysteine more than folic acid alone.⁷⁷ Homocysteine levels of individuals with homozygous MTHFR genotype were particularly sensitive to the status of several B vitamins (B2, B12 and B6).⁷⁸ An inverse relationship between riboflavin status and plasma homocysteine has also been observed, especially in those with the MTHFR polymorphism.^{79,80} Riboflavin supplementation has been shown to lower homocysteine⁸¹ and blood pressure^{82,83,84} in individuals homozygous for the MTHFR polymorphism. A combination of B vitamins (B2, B6, B12) in addition to folate supplementation has also shown to significantly reduce plasma homocysteine concentrations in older patients.⁸⁵

Vitamin D

An inverse relationship has been found between homocysteine levels and Vitamin D concentration. Vitamin D may modulate the expression of genes involved in homocysteine metabolism.⁸⁶ In animal models, Vitamin D deficiency has also been shown to impair the synthesis of folate transport protein necessary for folate absorption across the intestine.⁸⁷ Adequate Vitamin D is associated with reduced incidence of neovascular AMD, wet macular degeneration, and reduced subretinal fibrosis in wet macular degeneration.^{88,89,90}

Zinc

A number of the enzymes that are involved in homocysteine and methionine metabolism are zinc metalloenzymes. Therefore, a serum zinc deficiency can reduce the activity of the enzymes and therefore increase serum homocysteine levels.⁹¹ Zinc supplementation has been shown to reduce plasma homocysteine levels by eliminating zinc deficiency.⁹²

Other Synergistic Ingredients

Vitamins and N-Acetyl Cysteine

Since homocysteine induces oxidative stress, antioxidants such as Vitamin E, C, and N-Acetylcysteine (NAC, a precursor of the body's natural glutathione) are important synergistic dietary ingredients for protecting vascular retinal tissue from oxidative

damage. Cellular models have confirmed this. Vitamin C has been shown to modulate oxidative stress in human retinal pigment epithelium.⁹³ Vitamin C and Vitamin E help compensate for the glutathione depletion against pro-oxidants in lens cells.⁹⁴ NAC, Vitamin C, and Vitamin E have been shown to significantly attenuate homocysteine-induced damage.⁹⁵ Pantothenic acid (sometimes referred to as Vitamin B₅) is found in the body in the form of Coenzyme A (CoA), which is involved in the synthesis of glutathione.⁹⁶ Vitamin B₁ (Thiamine) also indirectly acts as an antioxidant.^{97,98}

Lutein and Zeaxanthin

The carotenoid pigments, lutein and zeaxanthin also have antioxidant activity that has been shown to have specific effect against oxidative stress in the macula of the eye. These carotenoids ameliorate light and oxygen damage, preventing age-related cellular and tissue deterioration in the eye.⁹⁹ Epidemiologic studies suggest that insufficient dietary lutein and zeaxanthin intake or lower serum zeaxanthin levels are associated with increased risk for AMD by blocking harmful blue light and quenching reactive oxygen species and improving intracellular redox status.^{100,101}

Minerals

The minerals Copper and Zinc also play vital roles in retinal function and are essential for antioxidant defense mechanism in retinal tissue. Zinc and copper levels in the retinal pigment epithelium (RPE) and choroid complex of patients with AMD were found to be lower than in patients without AMD.¹⁰² Selenium is a trace element that also functions as an antioxidant through the selenium-containing enzyme glutathione peroxidase, a vital antioxidant enzyme found in all cells with specific activity against hydrogen peroxide. Deficiencies in selenium have been associated with lowered activity of this antioxidant enzyme.¹⁰³ In addition, selenium has been shown in animal studies to be a unique requirement for protecting the microvasculature of the retina.¹⁰⁴

3. Dosage and Administration

The recommended adult dose of Ocufolin is 1 capsule orally per day (with a meal) or as recommended by your health care practitioner based on an assessment of metabolic imbalances. Ocufolin is not recommended for use with children or during pregnancy. Ocufolin must be administered under medical supervision.

Each capsule contains:

Folate (as (6S)-5-methyltetrahydrofolic acid, calcium salt)	900 mcg
Vitamin C (Ascorbic Acid)	33.3 mg
Vitamin D (as Cholecalciferol)	1500 IU
Vitamin E Natural Tocopherols (as Alpha, Beta, Gamma, & Delta)	7.5 IU
Vitamin B ₁ (As Thiamine Hydrochloride)	1.5 mg
Vitamin B ₂ (Riboflavin)	10 mg
Vitamin B ₆ (as Pyridoxal-5-Phosphate)	3 mg
Vitamin B ₁₂ (as Methylcobalamin)	500 mcg
Pantothenic Acid (as Calcium-D-Pantothenate)	5 mg
Zinc (as Zinc Oxide)	26.6 mg

Selenium (as L- Selenomethionine)	20 mcg
Copper (as Cupric Oxide)	0.667 mcg
N-Acetyl Cysteine (NAC)	180 mg
Lutein	3.35 mg
Zeaxanthin	700 mcg

Other Ingredients: Capsule (Hypromellose & Gellan Gum) Dicalcium Phosphate, Rice Flour, Magnesium Stearate.

Contains Soy.

Metafolin® is a registered trademark of Merck KGaA, Darmstadt, Germany.

4. Contraindications

Ocufolin is contraindicated in patients with known hypersensitivity to any of the components contained in this product. Ocufolin contains folate, which may interact with certain drugs that interfere with folate absorption or metabolism of homocysteine. Consult your healthcare professional (e.g., doctor or pharmacist) for more information. If you are pregnant or breastfeeding, check with a doctor before using Ocufolin.

5. Adverse Effects

Allergic reactions to L-methylfolate are rare. However, get medical help right away if you notice any symptoms of a serious allergic reaction, including: rash, itching/swelling, dizziness or trouble breathing. Nausea, vomiting, headache, other gastrointestinal symptoms, and rash have been associated with NAC. There are rare reports of renal stone formations with NAC. There are also rare reports of anxiety and elevation in blood pressure resulting from supplementation with combination B vitamins in patients with a history of anxiety attacks or panic disorders.

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