

FOLZIN-5[®] Tablet: The Active form of folate with added advantage of Zinc

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ABSTRACT

FOLZIN-5 Tablets contain the body's preferred form of folate with added advantage of zinc, which play a key role in a variety of biochemical reactions that are required for normal cell division and repair. Folate is the generic term comprising all the various chemical folate forms, which are water soluble B-vitamins, and also include synthetic provitamin folic acid. LMF is highly bioavailable source of folic acid. It is the natural, active form of folic acid which is an integral component of prenatal care, homocysteine management, depression treatment, dementia and cardiovascular concerns. LMF is a vitamin essential for reproductive health. The present paper Reviews the Role of **FOLZIN-5[®] Tablets** developed by R&D cell of ELARYK PHARMACEUTICALS NEW DELHI for prevention & treatment of disorders including Anaemia, neural tube defects (NTDs), cardiovascular diseases (CVD) & Alzheimer's disease.

Keywords: FOLZIN-5[®] Tablets, L-methylfolate, Zinc, Anaemia, Neural tube defects (NTDs), Cardiovascular diseases (CVD), Alzheimer's disease.

INTRODUCTION

L-methylfolate or 6(S)-5-methyltetrahydrofolate [6(S)-5-MTHF], is the primary biologically active diastereoisomer of folate and the primary form of folate in circulation. It is also the form which is transported across membranes into peripheral tissues, particularly across the blood brain barrier. In the cell, 6(S)-5-MTHF is used in the methylation of homocysteine to form methionine and tetrahydrofolate (THF). THF is the immediate acceptor of one carbon units for the synthesis of thymidine-DNA, purines (RNA and DNA) and methionine. About 70% of food folate and cellular folate is comprised of 6(S)-5-MTHF. Folic acid, the synthetic form of folate, must undergo enzymatic

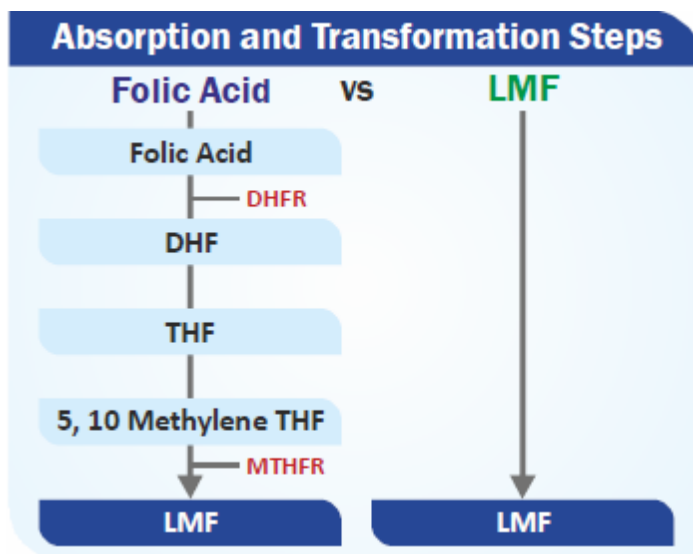
reduction by methylenetetrahydrofolate reductase (MTHFR) to become biologically active. Genetic mutations of MTHFR result in a cell's inability to convert folic acid to 6(S)-5-MTHF. [1]

Importance of l-methyl folate & its deficiency

L-Methyl Folate is a bio active form of water soluble B vitamin (B9), one of the 13 essential vitamins required for several important biological processes, which include-

- Normal cell growth and replication
- Nucleic acid synthesis
- Red blood cell maturation
- DNA repair
- Modulation of the amino acid homocysteine
- Brain development [2]

Folic acid and LMF



Regular folic acid undergoes a 4-step enzymatic conversion process to achieve LMF - the active form of folic acid used by the body. Dihydrofolate Reductase (DHFR) converts folic acid to dihydrofolate (DHF), DHF is then converted to tetrahydrofolate (THF), THF is converted to 5,10-methylene THF, and the last conversion step involves an enzyme Methylenetetrahydrofolate Reductase (MTHFR) converting 5,10-methylene THF to LMF. [3]

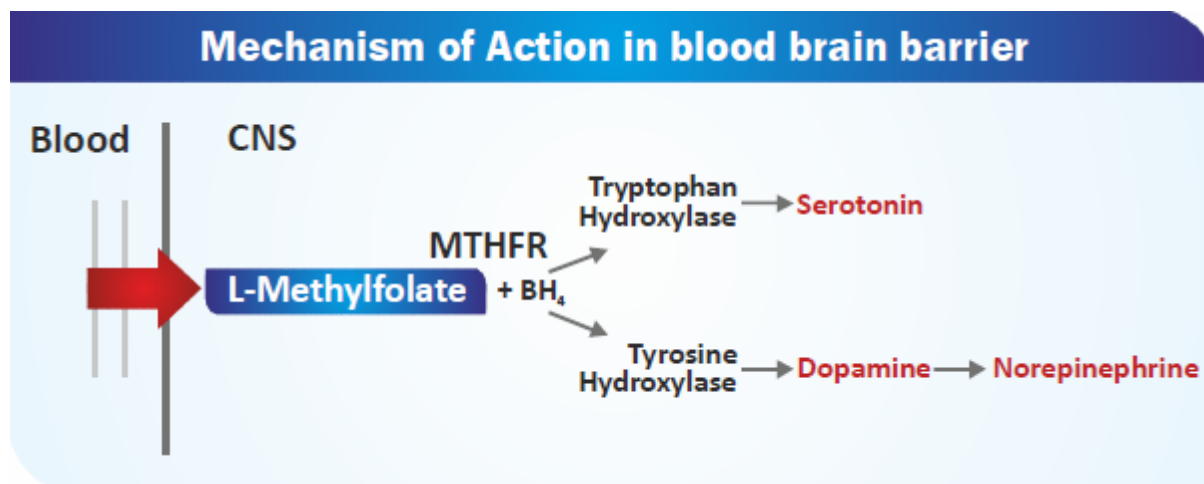
However research has shown that the conversion of folic acid into LMF is frequently disrupted by genetic factors, age-related problems, medications and metabolic disturbances. [4]

- Large number of people (almost 20-40%) have a MTHFR genotype variation and are unable to fully convert regular folic acid to LMF.

- Limited absorption results in a significant reduction in the amount of LMF made available to the body; limiting the ability to build and maintain healthy reserves of folic acid and significantly increasing risk of birth defects, homocysteine build up and depression.
- Inability of folic acid to cross the blood brain barrier has also limited its use in the treatment of depression where Folate deficiency has also been found to be widespread. [5-9]

Mechanism of action

L-Methyl Folate deficiency has also been linked to courses of depressions that are more severe, longer in duration, and treatment resistant. A deficiency may result in inadequate CNS synthesis of serotonin, norepinephrine, and dopamine.



L- Methylfolate developed by Puneet Laboratories is the optically bioactive L-form having specific optical rotation between +34 ° to +42 °

- Functions as a methyl donor and monoamine synthesis modulator
- Regulates tetrahydrobiopterin (BH4), a critical enzyme cofactor for trimonoamine neurotransmitter synthesis
- Methyl donor for DNA methylation and thus an epigenetic regulator
- Involved in critical enzymatic reactions throughout the body
- By depleting excess homocysteine, folate benefits cardiovascular health and nervous system function

Composition

Each folzin-5® tablet contains

L-Methyl folate- 5 mg

Zincbisglycinate (Eq.to elemental Zinc)- 25 mg

Pregnancy health



Supplementation with L-Methyl folate is internationally recommended to women from the moment they are trying to conceive until 12 weeks of pregnancy. Due to the inability of some women to convert folic acid to L-Methylfolate due to gene characteristics, L-Methyl folate provides an effective

Clinical applications

Due to its unique ability to provide the complete nutritional benefit of folate supplementation, L-Methyl folate provides an effective folate supplementation in the following conditions:

- Fertility support
- Prenatal care
- Cardiovascular diseases
- Diabetic neuropathy
- Dementia
- Depressive disorders

L-Methyl folate has been linked to benefits of augmenting anti-depressant effect, addressing early memory loss, improving sensation with diabetic peripheral neuropathy and reducing the risks of neural tube defects.

folate supplementation during pregnancy for preventing complications in both mother and foetus. Which include miscarriages, neural tube defects, congenital heart disease, oral clefts and possibly preterm birth.

Cardiovascular health



L-Methyl Folate is involved in critical enzymatic reactions throughout the body. Deficiency of folate in the body systems can lead to development of a substance called homocysteine, responsible for cardiovascular decline. L-Methyl folate benefits cardiovascular health by reducing the levels of homocysteine.

Diabetic neuropathy

Diabetic peripheral neuropathy (DPN) has been estimated to affect roughly half of all patients with type 2 diabetes mellitus. Elevated levels of

homocysteine and reduced bioactivity of nitric oxide induce endothelial dysfunction, endothelial injury, and may impair vasodilation in patients with diabetic neuropathy. L-Methyl folate has been shown to be more bioavailable and effective in lowering homocysteine levels than naturally occurring folic acid when combined with methylcobalamin and pyridoxal 5 phosphate. In this combination, L-Methyl folate has been found to be effective for alleviating signs and symptoms of DPN, including anaesthesia, motor neuropathy, and autonomic neuropathy.

Depressive disorders



Lower systemic levels of L-Methyl Folate can result from poor dietary intake, diabetes, various gastrointestinal disorders, hypothyroidism, renal failure, nicotine dependence, alcoholism, and a particular genetic polymorphism prevalent in 70% of depressed patients.

How the Drug Works

L-Methyl folate is active form of a water-soluble B vitamin (B9) that is essential for cell growth/ reproduction, breakdown/ utilization of proteins, formation of nucleic acids, and other functions

- L-methylfolate, or 6-(S)-5-methyltetrahydrofolate, is derived from folate and is the form that enters the brain and works directly as a methyl donor and monoamine synthesis modulator
- That is, it regulates tetrahydrobiopterin (BH4), a critical enzyme cofactor for trimonoamine neurotransmitter synthesis
- Methyl donor for DNA methylation and thus an epigenetic regulator

Clinical Study Reports of L-Methyl Folate in Folin-5 Tablets

L-methylfolate Can Help Treat Depression

In a study (DB-RCT) of 123 patients with either depression or schizophrenia, a large portion of them had folate deficiencies.

Patients with folate deficiencies were given either methylfolate or placebo. The patients given methylfolate improved significantly compared to placebo both clinically and socially, especially in mood, and the difference in improvements increased with time.

In a study (DB-RCT) of 68 depression patients who did not respond to antidepressants (selective serotonin reuptake inhibitors, or SSRI), 15 mg/day of L-methylfolate was given for 12 months. Of the 68 patients, 26 had a full recovery from their depression and 35 experienced a reduction in the severity of their depression (remission).

L-Methylfolate Can Help Those with Bipolar 1 Depression

The Montgomery Asberg Depression Rating Scale (MADRS) is used to measure the degree of depression in patients with a higher score number being worse.

In a study of 10 patients with bipolar depression, L-methylfolate in combination with conventional treatment reduced the average MADRS score from 23.4 to 13.9.

Six out of the 10 patients showed at least a 50% improvement in MADRS score and the other four experienced a reduction in the severity of their depression (remission).

L-methylfolate Can Help With Schizophrenia

In a study of 91 schizophrenic patients, there was a link between the severity of the negative symptoms of schizophrenia and low blood levels of folate .

It was hypothesized that the link was due to poor diet and more cigarette smoking in schizophrenic patients.

Indeed, cigarette smoking was linked to decreased levels of folate .

In a study (DB-RCT) of 140 schizophrenic patients, only those given folic acid with vitamin B12 supplementation (and a specific mutation of the FOLH1 gene) improved negative symptoms considerably. The FOLH1 gene is one of the genes responsible for metabolizing methylfolate .

All the patients in the previously mentioned study had been on antischizophrenic drugs for six months prior or longer but had shown no improvements in symptoms.

In another study (DB-RCT) of 35 schizophrenic patients, L-methylfolate not only improved symptoms but also produced beneficial changes in the brain.

The patients given L-methylfolate supplements showed increased cortical thickness in the medial prefrontal cortex (mPFC), which was correlated to a partial restoration of structure and function of the mPFC.

The medial orbitofrontal cortex (mOFC), which normally deactivates during tasks requiring working memory, is dysfunctional in schizophrenic patients. The patients receiving L-methylfolate supplementation showed increased deactivation.

Schizophrenia can be due to many different factors. This is the reason why one of the studies only found positive effects in those with FOLH1 gene mutations.

L-methylfolate can help with alzheimer's disease

People with Alzheimer's disease are more likely to have reduced folate levels compared to healthy people. Therefore, L-methylfolate supplements can improve symptoms in those patients.

Alzheimer's disease is also brought about by increased inflammation in the brain due to higher levels of tumor necrosis factor (TNF)- α , an inflammatory molecule, and amyloid beta plaques. In a study (SB-RCT) of 121 patients, L-methylfolate greatly reduced levels of TNF- α and amyloid beta.

In a recent clinical trial of 30 Alzheimer's and dementia patients, L-methylfolate greatly reduced brain deterioration in the hippocampus and cortical areas of the brain.

The conversion of homocysteine slowed brain deterioration and improved cognitive functions such as learning and memory. The study indicated that treatment for at least one year is usually necessary to slow decline.

L-methylfolate can reduce mania

Mania is a state of heightened arousal, elevated mood, and increased energy. The Young Mania Rating Scale (YMRS) is used to score mania with higher numbers signifying worse mania.

In a study of 10 manic and bipolar depressed patients, L-methylfolate reduced the average pre-treatment YMRS from 3.2 to 2.7.

L-methylfolate improves pregnancy outcomes

L-methylfolate is crucial for pregnant women as it helps **reduce the risk of developing different disorders that can occur in both the fetus and the mom**. Because of the importance of supplementation, the U.S. government began mandating the addition of more folic acid into grain products (140 μ g/100g) in January 1998.

L-Methylfolate supplementation prevents recurrent miscarriage

L-methylfolate supplementation is essential for pregnant women as it helps reduce the risk of recurrent miscarriage by reducing homocysteine level.

L-Methylfolate Supplementation can Help Prevent Neural Tube Defect (NTD)

L-Methylfolate supplementation helps prevent neural tube defect, which are defects of the brain, spine, and spinal cord.

It is advised for women that are more at risk for NTD to take 5mg daily and all other pregnant women to take 0.4-1mg daily.

L-Methylfolate Supplementation can Help Prevent Anemia

Pregnant women usually have reduced hemoglobin (protein that carries oxygen in the blood) levels, which leads to anemia in 5% of pregnancies.

In a study of 58 pregnant women taking prenatal supplements along with L-methylfolate had significantly higher hemoglobin levels at the time of delivery than 54 women only taking prenatal supplements.

L-methylfolate may prevent preterm birth

Low blood folate levels have been linked to shorter pregnancy times. A study of 34,480 women found that supplementing with L-methylfolate for longer than one year significantly decreased the chances of preterm birth. The length of L-methylfolate supplementation (> 1 year) was equally as important as supplementing itself.

Supplementing with L-methylfolate has also been shown to reduce risks of other pregnancy problems such as heart defects and orofacial clefts, which are openings that may form in the mouth and lip.

L-Methylfolate Can Boost the Immune System

T cells are key cells involved in the innate immune system, the part of the immune system that provides short-term defense against pathogens. A cell study showed that folate deficiency led to decreased production of T-cells.

Increasing folate levels increased the T-cell levels to normal levels. Other studies have shown that deficiencies in folate also lead to decreased responses of T-cells and antibodies to certain pathogens. This ultimately leads to decreased resistance to infections.

L-methylfolate may improve autism

Mutations in the gene encoding the enzyme 5, 10-methylenetetrahydrofolate (MTHFR) disrupt the enzyme's ability to convert folic acid into L-methylfolate. L-methylfolate decreased symptoms of

aggressive and disruptive behavior in an autistic child with an MTHFR C667T mutation.

Role of Zinc in Folzin-5 Tablets

Zinc is called an "essential trace element" because very small amounts of zinc are necessary for human health. Since the human body does not store excess zinc, it must be consumed regularly as part of the diet. Zinc is needed for the proper growth and maintenance of the human body. It is found in several systems and biological reactions, and it is needed for immune function, wound healing, blood clotting, thyroid function, depression, depression after pregnancy (postpartum depression), dementia, dry mouth, attention deficit-hyperactivity disorder (ADHD), blunted sense of taste (hypogeusia), hepatic encephalopathy, alcohol-related liver disease, Crohn's disease, ulcerative colitis, inflammatory bowel disease, canker sores, stomach ulcers, leg ulcers, and bed sores.

Precautions

General

When administered in daily doses above 0.1mg, may obscure the detection of B deficiency (specifically, the administration of folic acid may reverse the hematological manifestations of B deficiency, including pernicious anemia, while not addressing the neurological manifestations).

FOLZIN-5® Tablets may be less likely than folic acid to mask vitamin B deficiency. L-Methyl folate therapy alone is inadequate for the treatment of a B deficiency. A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed, (although not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of a precipitation of a mixed/manic episode in patients at risk for bipolar disorder.

FOLZIN-5® Tablets is not an antidepressant; however, 5-MTHF has been shown to enhance antidepressant effects of known antidepressants. Caution is recommended in patients with a history of bipolar illness. Patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder since mood elevation in this population is possible.

PHARMACOKINETICS

Absorption and Elimination

L-methylfolate is a water soluble molecule which is primarily excreted via the kidneys. In a study of subjects with coronary artery disease (n=21), peak plasma levels were reached in 1-3 hours following oral/parenteral administration. Peak concentrations of L-methylfolate were found to be more than seven times higher than folic acid (129 ng ml⁻¹ vs. 14.1 ng ml⁻¹) following ORAL/PARENTERAL administration. The mean elimination half-life is approximately 3 hours after 5mg of oral L-methylfolate, administered daily for 7 days. The mean values for C_{max}, T_{max}, and AUC₀₋₁₂ were 129 ng ml⁻¹, 1.3 hr., and 383 respectively.

Distribution

Red blood cells (RBCs) appear to be the storage depot for folate, as RBC levels remain elevated for periods in excess of 40 days following discontinuation of supplementation. Plasma protein binding studies showed that L-methylfolate is 56% bound to plasma proteins.

Indication and usage

FOLZIN-5 tablets are indicated for treatment or prevention of low folate levels. Low folate levels can lead to certain types of anemia. Conditions that can cause low folate levels include poor diet, pregnancy, alcoholism, liver disease, certain stomach/intestinal problems, kidney dialysis, among others. Women of childbearing age should receive adequate amounts of folic acid either through their diet or supplements to prevent infant spinal cord birth defects.

Contraindications

There have been rare reports of hypersensitivity (allergic-like reactions) to **FOLZIN-5**. Therefore, a known hypersensitivity to any of the components in the product is a contraindication to its use for any indication.

Drug interactions

FOLZIN-5 added to other Drugs: High dose folic acid may result in decreased serum levels for pyrimethamine and first generation anticonvulsants (carbamazepine, fosphenytoin, phenytoin, phenobarbital, primidone, valproic acid, valproate). Antibiotics may alter the intestinal microflora and may decrease the absorption of methylcobalamin.

Cholestyramine, colchicines or colestipol may decrease the enterohepatic re-absorption of methylcobalamin.

FOLZIN-5® Tablets contains folate, which may have interactions the following:

Antiepileptic drugs (AED): The AED class including, but not limited to, phenytoin, carbamazepine, primidone, valproic acid, phenobarbital and lamotrigine have been shown to impair folate absorption and increase the metabolism of circulating folate. Additionally, concurrent use of folic acid has been associated with enhanced phenytoin metabolism, lowering the level of this AED in the blood and allowing breakthrough seizures to occur. Capecitabine: Folinic acid (5-formyltetrahydrofolate) may increase the toxicity of Capecitabine.

Dihydrofolate Reductase Inhibitors (DHFRIs): DHFRIs block the conversion of folic acid to its active forms, and lower plasma and red blood cell folate levels. DHFRIs include aminopterin, methotrexate, pyrimethamine, triamterene, and trimethoprim. Fluoxetine: Fluoxetine exerts a noncompetitive inhibition of the 5-methyltetrahydrofolate active transport in the intestine.

Isotretinoin: Reduced folate levels have occurred in some patients taking isotretinoin, Nonsteroidal Anti-inflammatory Drugs (NSAIDs): NSAIDs have been shown to inhibit some folate dependent enzymes in laboratory experiments. NSAIDs include ibuprofen, naproxen, indomethacin and sulindac. Oral Contraceptives: Serum folate levels may be depressed by oral contraceptive therapy. Methylprednisolone: Reduced serum folate levels have been noted after treatment with methylprednisolone.

Pancreatic Enzymes: Reduced folate levels have occurred in some patients taking pancreatic extracts. Pentamidine: Reduced folate levels have been seen with prolonged intravenous pentamidine. Metformin treatment in patients with type 2 diabetes decreases serum folate. Warfarin can produce significant impairment in folate status after a 6-month therapy.

Adverse reactions

While allergic sensitization has been reported following both oral and parenteral administration of folic acid, allergic sensitization has not been reported with the use of **FOLZIN-5**. Paresthesia, somnolence, nausea and headaches have been reported with

pyridoxal 5'-phosphate. Mild transient diarrhea, polycythemia vera, itching, transitory exanthema and the feeling of swelling of the entire body has been associated with methylcobalamin.

Dosage and administration

The recommended dose is one tablet twice daily (B.I.D.) or as directed. under medical supervision.

Advantages of 5 mg of L-Methylfolate Vs 1 mg of L-Methylfolate

It is advised to take 5mg of L-Methylfolate daily as against 1mg daily as in most clinical studies higher dose is found to be more effective in lowering homocysteine level.

Storage: Store at controlled room temperature 15°C to 30°C (59°F to 86°F) Protect from light and moisture.

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