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LACTOFOLIN® Tablet: The preferred form of folate

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ABSTRACT

Lactofolin Tablets (**5- M**ethyl**T**etra**H**ydro**F**olate (**5-MTHF**)) contain the body's preferred form of folate, 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 Lactofolin tablets developed by R&D cell of Lactonova Nutripharm Pvt Ltd. Hyderabad for prevention & treatment of disorders including Anaemia, neural tube defects (NTDs), cardiovascular diseases (CVD) & Alzheimer's disease.

Keywords; Lactofolin®Tablets, L-methylfolate, 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.

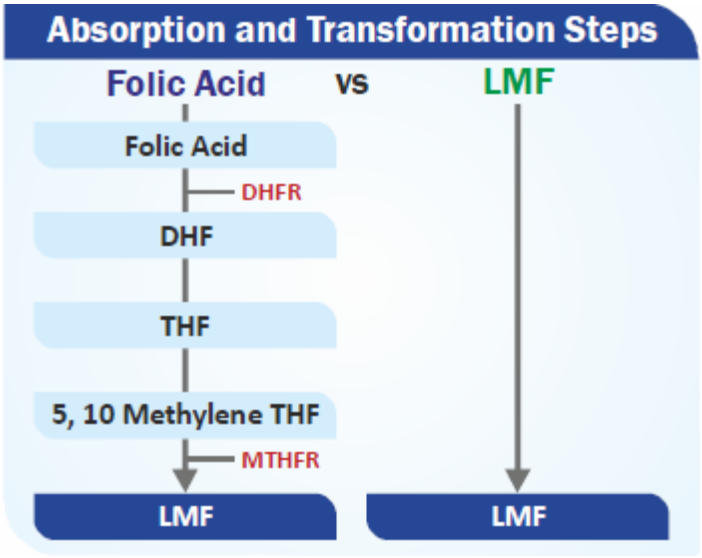
IMPORTANCE OF L-METHYL FOLATE & ITS DEFICIENCY

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

Folic acid and LMF



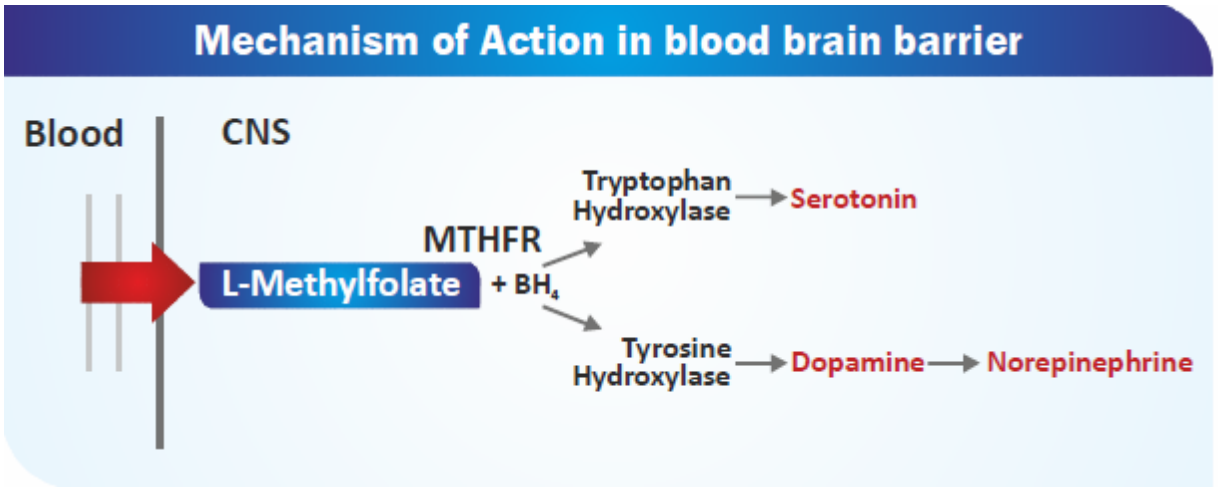
Regular folic acid undergoes a 4-step enzymatic conversion process to achieve LMF - the active form of folic acid used by the body. Dihydrofolate Reductase (DHFR) converts folic acid to dihydrofolate (DHF), DHF is then converted to tetrahydrofolate (THF), THF is converted to 5,10-methylene THF, and the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

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.

- 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.

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

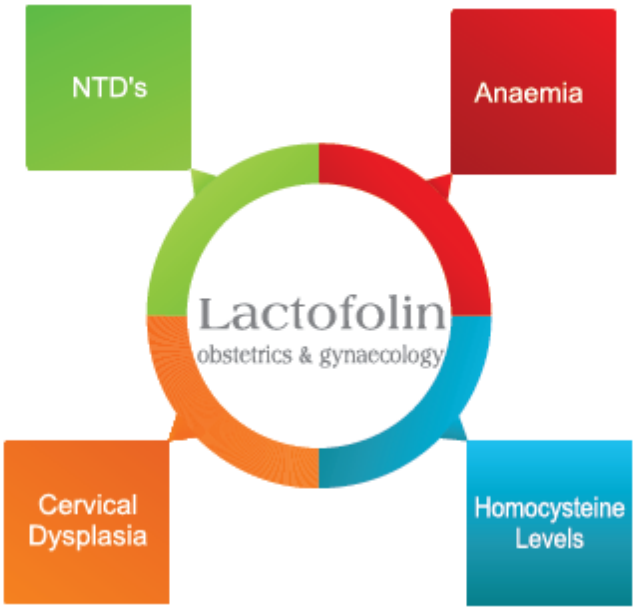
COMPOSITION

CLINICAL APPLICATIONS

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

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

The active form of folate, LMF 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.



Pregnancy health

Supplementation with folic acid 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, LMF provides an effective 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. LMF 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. LMF 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, LMF 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

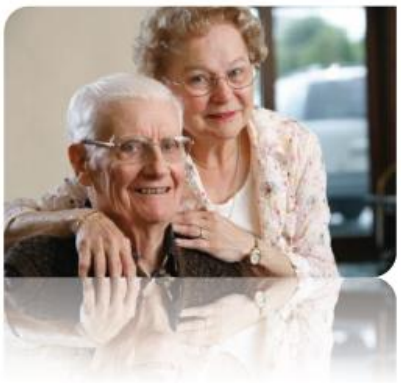
- Folate is a water-soluble B vitamin (B9) that is essential for cell growth/ reproduction, breakdown/ utilization of proteins, formation of nucleic acids, and other functions
- L-methylfolate, or 6-(S)-5-methyltetrahydrofolate, is derived from folate and is the form that enters the brain and works directly 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

Supporting Research Studies:

OBSTETRICS & GYNAECOLOGY

- Preconceptional folic acid supplementation for 8 weeks significantly reduces the occurrence of NTDs
  -AM J Clin Nutr 1996;63:520-525 & Int J Vitam Nutr Res 1995;65:267-271
- In a group of adolescent women, supplementation with above 400 mcg 5-MTHF daily for 24 weeks resulted in higher RBC folate levels compared to folic acid supplementation *-AM J Clin Nutr 2006;84:156-161*
- In a study folic acid supplementation (above 1 mg folic acid daily for 3 months) reverses cervical dysplasia in women taking oral contraceptives
  - AM J Clin Nutr 1982;35:73-82

CARDIOVASCULAR HEALTH



- In cardiovascular disease subjects, evidence suggests folic acid supplementation significantly reduces higher homocysteine levels *-Arch Intern Med 2001;161:695-700.*
- 5-MTHF improves blood flow by increasing NO synthesis in vascular endothelial, the net effect of which improvement in peripheral blood flow and lowering blood pressure *- J Physiol Heart Circ Physiol 2002;282:H2617-H2172*
- In a 6 week randomized study of 10 patients with coronary artery disease, 5-MTHF significantly improved flow mediated dialation (FMD) at the brachial artery
  -Arterioscler Thromb Vasc Biol 2001;21:1196-1202

NEUROPSYCHIATRIC APPLICATIONS

- Lower serum and RBC folate concentrations have an association with depression and deficiency might predict a poorer response to some antidepressant medications. Documented studies show improvement in such patients with on subsequent oral administration of 5-MTHF at higher than 1 mg doses daily for 6 - 12 months.
  Appl Neurophysiol 1979;42:171-183

PRECAUTIONS

General

Folic acid, 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).

L-METHYLFOLATE Tablets may be less likely than folic acid to mask vitamin B deficiency. 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.

L-METHYLFOLATE 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 Cmax, Tmax, 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

Lactofolin tablets are indicated for the distinct nutritional requirements of patients with endothelial dysfunction who present with loss of protective sensation and neuropathic pain associated with diabetic peripheral neuropathy.

Contraindications

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

Drug interactions

Lactofolin 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.

L-METHYLFOLATE 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 (DHFRI): DHFIs block the conversion of folic acid to its active forms, and lower plasma and red blood cell folate levels. DHFIs 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 methylpredinisolone.

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 Lactofolin. 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.

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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