DEPLIN® Tablets

DESCRIPTION

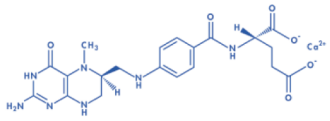
DEPLIN® is an orally administered medical food for use only under medical supervision for the dietary management of suboptimal folate levels in depressed patients or hyperhomocysteinemia in schizophrenia patients.

Each round coated light blue colored (7.5 mg) or oval scored coated orange colored (15 mg) tablet contains:

Dietary Ingredients:
L-methylfolate Calcium (as Metafolin®)*

*CAS#129025-21-4

Chemical Structure:



Ingredients:

7.5 mg
Dibasic Calcium Phosphate Dihydrate, Silicified Microcrystalline Cellulose 90, Silicified Microcrystalline Cellulose HD 90, Opadry II Blue 85F90748 (Polyvinyl Alcohol, Titanium Dioxide [color], PEG 3350, Talc and FD&C Blue #2[color]), L-methylfolate Calcium, Magnesium Stearate (Vegetable Source), and Carnauba Wax.

15mg
Dibasic Calcium Phosphate Dihydrate, Silicified Microcrystalline Cellulose 90, Opadry II Orange 85F43102, (Polyvinyl Alcohol, Titanium Dioxide [color], PEG 3350, Talc, FD&C Yellow #6[color], FD&C Yellow #5[color], FD&C Red #40[color] and FD&C Blue #2[color]), L-methylfolate Calcium, Magnesium Stearate (Vegetable Source), and Carnauba Wax.

DEPLIN® tablets do not contain sugar, lactose, yeast or gluten.

CLINICAL PHARMACOLOGY

L-methylfolate or 6(S)-5-methyltetrahydrofolate [6(S)-5-MTHF], is the primary biologically active isomer of folate[1] and the primary form of folate in circulation.[2] It is also the form which is transported across membranes into peripheral tissues[3], particularly across the blood brain barrier,[4] in contrast to folic acid which does not. In cells, 6(S)-5-MTHF is used in the methylation of homocysteine to form methionine and tetrahydrofolate (THF).[1] THF is the immediate acceptor of one carbon units for the synthesis of thymidine-DNA, purines (RNA and DNA) and methionine.[5] Folic acid, the synthetic form of folate, must undergo enzymatic reduction by methylenetetrahydrofolate reductase (MTHFR) to become biologically active.[6] Genetic mutations of MTHFR result in a cell's inability to convert folic acid to 6(S)-5-MTHF.[7]

Metafolin® (L-methylfolate calcium) is a substantially diastereoisomerically pure source of L-methylfolate containing not more than 1% D-methylfolate which results in not more than 0.075 milligrams (7.5mg) or 0.15 milligrams (15mg) of D-methylfolate in Deplin®.

D-methylfolate or 6(R)-5-methyltetrahydrofolate [6(R)-5-MTHF] is the other diastereoisomer of folate. Studies administering doses of 2.5 mg per day or higher resulted in plasma protein binding of D-methylfolate higher than L-methylfolate causing a significantly higher renal clearance of L-methylfolate when compared to D-methylfolate.[8] Further, D-methylfolate is found to be stored in tissues in the body, mainly in the liver. D-methylfolate is not metabolized by the body and has been hypothesized to inhibit regulatory enzymes related to folate and homocysteine metabolism and reduces the bioavailability of L-methylfolate.[9]

Pharmacokinetics[9,10]:
Absorption and Elimination: L-methylfolate is a water soluble molecule which is primarily excreted via the kidneys.[10] In a study of subjects with coronary artery disease (n=21), peak plasma levels were reached in 1-3 hours following ORAL/PARENTERAL administration.[9] 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 D, L-methylfolate. The mean values for C_{max}, T_{max}, and AUC_{0-12} 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.[10] Plasma protein binding studies showed that L-methylfolate is 56% bound to plasma proteins.[9]

INDICATIONS AND USAGE

ADJUNCTIVE USE IN MAJOR DEPRESSIVE DISORDER

DEPLIN® is indicated for the distinct nutritional requirements of individuals who have suboptimal L-methylfolate levels in the cerebrospinal fluid, plasma, and/or red blood cells and have major depressive disorder (MDD) with particular emphasis as adjunctive support for individuals who are on an antidepressant.[11-14]

ADJUNCTIVE USE IN SCHIZOPHRENIA

DEPLIN® is indicated for the distinct nutritional requirements of individuals who have or are at risk for hyperhomocysteinemia and have schizophrenia who present with negative symptoms and/or cognitive impairment, with particular emphasis as an adjunctive support for individuals who have stabilized on antipsychotics.[11]

DEPLIN® is indicated regardless of MTHFR C677T polymorphism genotype.[9]

DEPLIN® should always be used under medical supervision.

Clinical Studies:

ADJUNCTIVE USE OF MAJOR DEPRESSION

Methylfolate use as Adjunctive Therapy in Patients with Depression[11]: 5-MTHF (racemic) 15mg (7.5mg L-methylfolate) once daily has been studied as an adjunctive therapy among 24 depressed patients with low folate levels who were also taking either a tricyclic antidepressant (TCA) or a monoamine-oxidase inhibitor (MAOI) antidepressant. Under double-blind conditions, patients were randomized to receive either 5-MTHF or placebo as an adjunct to their MAOI or TCA antidepressant. 5-MTHF, combined with an antidepressant, was found to be significantly more effective than placebo in reducing depressive symptoms following 3 ($p<0.01$) as well as 6 months ($p<0.001$). 5-MTHF was well tolerated, with no serious adverse events reported.

Methylfolate Trials in Patients with Depression[12-14]: The role of 5-MTHF (monotherapy) for depression has been studied in two open label trials[13,14] and one randomized, double blind trial, active-comparator trials involving the use of the U.S. Food and Drug Administration (F.D.A.)-approved antidepressant trazodone.[14] The dose of 5-MTHF utilized was 50mg (25mg L-methylfolate) once daily for 6-8 weeks in two of the trials[12,13] or 30mg three times a day (15mg L-methylfolate) for 4 weeks in the third trial.[14] 5-MTHF was associated with a significant improvement in depressive symptoms compared to baseline in each of the three trials. ($p<0.05$[12], $p<0.0001$[13], $p<0.01$[14]) In addition, in the double-blind trial, 5-MTHF was associated with an antidepressant effect that was comparable in magnitude with the antidepressant effects of trazodone. In all three trials, 5-MTHF monotherapy was well tolerated with no serious adverse events reported.

The Relevance of the MTHFR C677T Polymorphism in Folate Metabolism and Depression:
Impact on Bioavailability: In a study involving 21 subjects, there was no difference in the bioavailability of L-methylfolate in the plasma with regards to the homozygous (T/T) and normal population (C/C) following administration of 5mg of D, L-methylfolate.[9]

Depression: In a meta-analysis[15] of 10 studies (11,709 participants; 1,280 cases of depression, 10,429 controls) there is an increase risk of depression among individuals who were homozygous for the TT genotype compared to normal controls (O.R. 1.36), In a study of depressed patients[16], (n=189) the thermolabile variant of MTHFR was significantly more common in the group with a history of depressive disorder ($p=0.03$) compared to controls (70% vs. 55% respectively).

ADJUNCTIVE USE OF SCHIZOPHRENIA

Methylfolate Trial in Patients with Schizophrenia:[11] 5-MTHF 15mg (7.5mg L-methylfolate) once daily has been studied as an augmentation (adjunctive) therapy among 17 schizophrenia patients with low or borderline low folate levels who were also taking antipsychotics. Under double-blind conditions, patients were randomized to receive either 5-MTHF or placebo as an adjunct to their antipsychotic. 5-MTHF , combined with an antipsychotic was found to be significantly more effective than placebo in reducing symptoms following 3 months ($p<0.01$) and 6 months ($p<0.001$). 5-MTHF was well tolerated with no serious adverse events reported.

CONTRAINDICATIONS

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

PRECAUTIONS

General:
Folic acid, when administered in daily doses above 0.1mg, may obscure the detection of B_{12} deficiency (specifically, the administration of folic acid may reverse the hematological manifestations of B_{12} deficiency, including pernicious anemia, while not addressing the neurological manifestations). L-methylfolate may be less likely than folic acid to mask vitamin B_{12} deficiency.[17,18] Folate therapy alone is inadequate for the treatment of a B_{12} deficiency.

Folic acid, when administered in daily doses above 800 mcg, may increase the amount of unmetabolized folic acid[2,19], which has been linked to accelerated growth of existing neoplasms in the colon. L-methylfolate may be less likely than folic acid to accelerate the growth of existing neoplasms.[6,20,21]

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. **Deplin®** is not an antidepressant; however, 5-MTHF has been shown to enhance antidepressant effects of known antidepressants.[11] 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.

Patient Information:
DEPLIN® is a medical food[22] for use under medical supervision and direction.

INTERACTION WITH DRUGS:

L-Methylfolate
No decrease in effectiveness of drugs has been reported with the use of **Deplin®** (L-methylfolate), however several drugs have been shown to interact with folic acid, folate metabolism, the absorption of folate, and the degradation of folate. Monitoring of folate levels may be necessary among patients who are receiving treatment with the drugs listed below.

The interactions below are based on folic acid drug interaction reports in scientific publications.[23-27]

Drugs which may interact with folate include:

- 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.
- Cholestyramine: Reduces folic acid absorption and reduces serum folate levels.
- Colestipol: Reduces folic acid absorption and reduces serum folate levels.
- Cycloserine: Reduces folic acid absorption and reduces serum folate levels.
- 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 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.
- Smoking and Alcohol: Reduced serum folate levels have been noted.
- Sulfasalazine: Inhibits the absorption and metabolism of folic acid.
- 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

Allergic reactions have been reported following the use of both oral and parenteral folic acid, as well as the use of oral L-methylfolate.

DOSAGE AND ADMINISTRATION

The usual adult dose is 7.5 to 15 mg daily with or without food or as directed under medical supervision.

HOW SUPPLIED

Tablets:

7.5 mg	Bottle of 30	Product Code # 0525-0410-30*
	Bottle of 90	Product Code # 0525-0410-90*
	Bottle of 7	Product Code # 0525-0410-07*

Light Blue, round, coated
Imprinted on one side with "PAL". Imprinted on the other side with "7.5".

15 mg	Bottle of 90	Product Code # 0525-0450-90*

Orange, scored oval, coated
Imprinted on one side with "deplin". Imprinted on the other side with "15".

*Pamlab LLC does not represent these product codes to be actual National Drug Codes (NDCs). NDC format codes are product codes adjusted according to standard industry practice to meet the formatting requirements of pharmacy and health insurance computer systems.

Storage:
Store at controlled room temperature 15°C to 30°C (59°F to 86°F) (See USP). Protect from light and moisture. Dispense commercial product (30 & 90 tablets) in original light-resistant container. Dispense sample product in original bottle.

PATENTS

Some or all of the following patents may apply:
U.S. Patent No. 5,059,595
U.S. Patent No. 5,538,734
U.S. Patent No. 6,011,040
U.S. Patent No. 6,271,374
U.S. Patent No. 6,441,168 and other pending patent applications.

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