L-METHYL-B6-B12 Tablets

DESCRIPTION
L-Methyl-B6-B12 is a medical food for the clinical dietary management of the metabolic imbalances associated with hyperhomocysteinemia that cannot be managed by diet modification alone. Dispense by prescription. Use under medical supervision.

Each round coated purple colored tablet contains:
Pyridoxal 5'-phosphate 35 mg
L-methylfolate Calcium 3 mg
Methylcobalamin 2 mg

Dietary Ingredients
Dibasic Calcium Phosphate Dihydrate, Microcrystalline Cellulose 90, PYRIDOXAL-5'-PHOSPHATE, Microcrystalline Cellulose HD 90, Opadry II Purple 40L10045 (Polydextrose, Titanium Dioxide, Hypromellose 3cP, Hypromellose 6cP, Glycerol Triacetate, Hypromellose 50cP, FD&C Blue #2, FD&C Red #40 and Polyglycol 8000), Microcrystalline Cellulose 50, Opadry II Clear Y-19-7483 (Hypromellose 6cP, Maltodextrin, Hypromellose 3cP, Polyglycol 400 and Hypromellose 50cP), L-METHYLFOlate CALCIum, Magnesium Stearate, METHYLCOBALAMIN, and Carnauba Wax.

Contains FD&C Blue #2 and FD&C Red #40.

Indications
Hyperhomocysteinemia of any etiology.

Intended Use
Medical foods are intended for the patient who has a limited or impaired capacity to ingest, digest, absorb, or metabolize ordinary foodstuffs or certain nutrients, or who has other special medically determined nutrient requirements, the dietary management of which cannot be achieved by the modification of the normal diet alone.

L-Methyl-B6-B12 is a specially formulated medical food for the dietary support of patients with hyperhomocysteinemia. It also is helpful in managing patients with high total homocysteine concentrations associated with malabsorption of vitamin B₁₂ or suboptimal intake of B vitamins.

L-Methyl-B6-B12 Tablets should always be used under medical supervision.

Background
Folic acid itself does not occur in nature; it is synthetic and lacks coenzyme activity. To be beneficial in human metabolism, orally administered folic acid must be absorbed through the brush border of the intestine and transferred to the liver where it is reduced to tetrahydrofolate (THF) form within the cell. L-5-methyl-tetrahydrofolate (5MTHF) is the predominant form of dietary folate and the only species normally found in the systemic circulation. Although 5MTHF does not occur in natural foodstuffs, it has been specially synthesized and formulated and is commercially available as the calcium salt.
5MTHF is at least as effective as folic acid in improving folate status as measured by blood concentration of folate and by functional indicators of folate status, such as plasma homocysteine. 5MTHF may have advantages over folic acid because it may reduce folate’s potential for masking vitamin B₁₂ deficiency; 5MTHF also may be associated with a reduced interaction with drugs that inhibit dihydrofolate reductase.²

Homocysteine (HCy) is an intermediary in amino acid metabolism. It is not a building block of protein itself, but is an integral part of methionine metabolism.³ Hyperhomocysteinemia (HHCy) is frequently associated with folate deficiency, and 5MTHF works in concert with vitamin B₁₂ as a methyl-group donor in the remethylation of homocysteine to methionine.⁴,⁵ In this way 5MTHF can act to reduce the amount of serum homocysteine.⁴

HHCy has been associated with a myriad of medical conditions, including those concerning folate deficiency,⁵ endothelial dysfunction,⁶-¹⁰ oxidative stress of endothelial cells,¹¹,¹² vascular dysfunction,⁵,¹³ pre-eclampsia,¹⁴,¹⁵ coronary artery disease,⁶,⁸,¹³ microvascular angina,¹² cardiovascular disease,⁷,¹⁶,¹⁷ wound healing,¹⁸ microvascular endothelium,¹⁹ and cerebral endothelium.²⁰ Most of these reports include discussions of a nitric acid synthase (NOS) mechanism for the pathophysiology, in which HHCy impairs NOS function.⁵-⁸,¹⁰-²⁰

HCy impairs the nitric oxide synthase pathway,¹⁷ and antagonizes Nitric Oxide (NO) production,¹²,¹⁶,¹⁸ and disrupts NO signaling.²⁰ HCy promotes oxidative stress in endothelial cells via an NOS-dependent mechanism.¹¹ Oxidative stress lowers the bioavailability of NO, presumably by impairing NOS.¹²,¹⁶ NO has been considered to be a mediator of the repair of oxidative stress damage.¹⁸ In particular, the endothelial cells of the cardiovascular and central nervous system tissues rely on NO for wound repair, and endothelium and microvascular integrity.¹²,¹⁸ When NOS activity is impaired by HCy, both a lack and an excess of NO can have important pathological implications.¹⁶

In one study, 5-MTHF had beneficial effects on endothelial function and decreased vascular superoxide production by improving NOS "coupling."¹⁰

5-MTHF uniquely counteracts the harmful effects of HHCy and provides nutritional support for patients who have medical conditions related to oxidative stress and impaired activity of inducible or endothelial NOS.

Vitamin B₆ plays an active role in the maintenance of normal HCY levels.²¹

Vitamin B₁₂ is a cofactor in the conversion of homocysteine to methionine (which in turn is required for the synthesis of S-adenosylmethionine, a universal methyl donor).²²,²³

Active and ongoing medical supervision is required for the clinical management of patients with HHCy.

CONTRAINDICATIONS

L-METHYL-B6·B12 is contraindicated in patients with known hypersensitivity to any of the components contained in this product.

Discontinue use if patient exhibits signs of hypersensitivity such as tachycardia, urticaria, or shortness of breath.

PRECAUTIONS

Folic acid, when administered in daily doses above 0.1 mg, may obscure the detection of vitamin B₁₂ deficiency, including pernicious anemia. L-METHYL-B6·B12 may be less likely than folic acid to mask vitamin B₁₂ deficiency.²

INTERACTIONS WITH DRUGS

Major interactions occur when L-methylfolate is co-administered with 5-fluorouracil or any of its
prodrugs (e.g., capecitabine, tegafur) and prescribed in combination with leucovorin. Co-administration with folate therapy may potentiate the pharmacologic effects of 5-fluorouracil (5-FU). The exact mechanism of interaction is unknown. Although enhancement of 5-FU cytotoxicity may be used to advantage in some cancer patients, increased toxicity should also be considered; a lower dosage of 5-FU or the prodrug may be required.\(^{24-31}\)

Patients should be monitored closely for potential toxicities of 5-FU such as neutropenia, thrombocytopenia, stomatitis, gastrointestinal hemorrhage, severe diarrhea, vomiting, cutaneous reactions, and neuropathy. Deaths from severe enterocolitis, diarrhea, and dehydration have been reported in elderly patients receiving weekly leucovorin and fluorouracil concomitantly with folates. [Leucovorin is a mixture of the diastereoisomers of the 5-formyl derivative of tetrahydrofolic acid (THF)].\(^{28,30}\)

Additionally, L-METHYL-B6-B12 has been known to show moderate interactions with:

Antiepileptic drugs

**Folic acid**

Co-administration with folate therapy may reduce the anticonvulsant effects of phenytoin, phenobarbital, primidone, and succinimides. The exact mechanism of interaction is unknown. Available data pertain primarily to phenytoin. Some investigators suggest that folic acid may serve as a cofactor in the metabolism of phenytoin, thus clearance is increased in the presence of folic acid. In one study, administration of folic acid for 14 days reduced the serum levels of phenytoin in normal subjects without significantly altering the bound fraction. Urinary excretion of phenytoin and its metabolite, meta-hydroxydiphenylhydantoin, was increased. In another study, three of four folate-deficient male patients receiving phenytoin monotherapy for epilepsy demonstrated a 7.5% to 47.6% decrease in total phenytoin plasma concentration following the addition of folic acid 1 mg/day for 180 or 300 days. Ratios of urinary metabolites to parent drug increased in these patients, suggesting an increase in phenytoin oxidative metabolism. The interaction is further supported by case reports describing subtherapeutic phenytoin levels and/or breakthrough seizures following the addition of folate therapy, including one case involving folinic acid (leucovorin). Limited data are available for phenobarbital and primidone. In one study, the addition of folic acid 15 mg/day increased the frequency and severity of seizures in 13 of 26 folate-deficient epileptic patients receiving two or more anticonvulsant drugs, including phenytoin, phenobarbital, and primidone. Nine of them required discontinuation of folic acid therapy. No data are available for other hydantoin.\(^{32-48}\)

**Vitamin B\(_6\)**

Some antiepileptic medications, including valproic acid, carbamazepine, and phenytoin, increase the catabolism rate of vitamin B\(_6\) vitamers, resulting in low plasma PLP concentrations and hyperhomocysteinemia.\(^{49,50}\) High homocysteine levels in antiepileptic drug users can increase the risk of epileptic seizures and vascular events like stroke, and reduce the ability to control seizures in patients with epilepsy. Additionally, patients usually take antiepileptic drugs for periods of years, which increases their risk of chronic vascular toxicity.

Conversely, some studies have shown that supplementing with pyridoxine 1200 mg/day for 12 to 120 days can reduce serum concentrations of phenytoin and phenobarbital.\(^{51,52}\) It is not known whether lower doses of pyridoxine have this effect.

**Antibiotics**

A broad spectrum antibiotic used to treat tuberculosis in combination with pyridoxal phosphate. Cycloserine increases urinary excretion of pyridoxine.\(^{53}\) Urinary loss of pyridoxine may exacerbate seizures and neurotoxicity associated with cycloserine.

**Monoamines**
Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs) as well as dopamine may be affected by L-methylfolate. L-methylfolate regulates the synthesis of serotonin, dopamine, and norepinephrine.54

Interference with homocysteine metabolism. Metformin, methotrexate, nicotinic acid, and fibric acid derivatives (used in certain dyslipidemias) can reduce plasma folate and B6 levels and raise plasma homocysteine levels.55,56

Arsenic Trioxide
Arsenic trioxide, an antineoplastic drug indicated for induction of remission and consolidation in patients with acute promyelocytic leukemia (APL) who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, and whose APL is characterized by the presence of a specific genetic defect. Arsenic trioxide can cause QT interval prolongation and complete atrioventricular block.57 Theoretically, use of arsenic trioxide during intensive vitamin B12 therapy for the treatment of megaloblastic anemia may potentiate the risk of cardiac arrhythmias (e.g. ventricular tachycardia and torsade de pointes) because of the hypokalemia that may develop during the early phase of vitamin B12 therapy (due to increasing potassium requirements as normal erythropoiesis is established.57

Chloramphenicol
Chloramphenicol, a bacteriostatic antibiotic, may interfere with vitamin B12 activity. A few case reports suggested that chloramphenicol might interfere with the red blood cell response to vitamin B12 in some patients.58,59

It is worth noting that chloramphenicol is no longer widely prescribed in the U.S. since it is required to carry the boxed warning "Bone marrow hypoplasia including aplastic anemia and death has been reported following topical application of chloramphenicol. Chloramphenicol should not be used when less potentially dangerous agents would be expected to provide effective treatment." Most NDAs approved for chloramphenicol have been discontinued.

Proton Pump Inhibitors and H2 Receptor Antagonists
Proton pump inhibitors, such as omeprazole and lansoprazole, are indicated for the treatment of gastroesophageal reflux disease and peptic ulcer disease. These drugs can interfere with the absorption of vitamin B12 release from food by slowing the release of gastric acid.60-62 It is unclear whether these drugs affect vitamin B12 status.63-66

Histamine H2 receptor antagonists, such as cimetidine, famotidine, and ranitidine, are indicated for the treatment of peptic ulcers. These drugs can interfere with the absorption of vitamin B12 from food by slowing the release of hydrochloric acid into the stomach.60-62 There is no evidence that H2 receptor antagonists promote vitamin B12 deficiency, even after long-term use.66

Paresthesia, somnolence, nausea and headaches have been reported with pyridoxal 5' phosphate. Chronic administration of 1 to 6 grams oral pyridoxine per day for 12-40 months can cause severe and progressive sensory neuropathy.69-73 Symptom severity appears to be dose dependent, and symptoms usually stop when vitamin B6 is discontinued as soon as the symptoms are noticed.

Other side effects from excessive B6 intake include painful, disfiguring dermatological lesions; photosensitivity, and gastrointestinal symptoms (e.g. nausea and heartburn).22,70,74

Orally administered vitamin B12 has no reported side effects.72,73

Dosage and Administration
The recommended dose is one tablet twice daily or as directed. L-Methyl-B6-B12 tablets must be used under medical supervision.
How Supplied
L-Methyl-B6-B12 is available as a round coated purple colored tablet, debossed with "V362" on one side and blank on the other. Commercial product is supplied in bottles of five hundred (500) tablets.

Commercial Product (500 tablets) 76439-362-50

Storage
Store at controlled room temperature 15°C to 30°C (59°F to 86°F) Protect from light and moisture. Dispense in tight, light-resistant container.

Patents
Some or all of the following patents may apply:

U.S. Patent No. 4,940,658
U.S. Patent No. 5,563,126
U.S. Patent No. 5,795,873
U.S. Patent No. 5,997,915
U.S. Patent No. 6,011,040
U.S. Patent No. 6,207,651
U.S. Patent No. 6,254,904
U.S. Patent No. 6,297,224
U.S. Patent No. 6,528,496
and other pending patent applications.

References

1 United States Food and Drug Administration Title 21 Code of Federal Regulations 101.90(j)(8).
11 Pimentel AM, Pereira NR, Costa CA, et al. L-Arginine-nitric oxide pathway and oxidative stress


26 "Product Information. Xeloda (capecitabine)." Roche Laboratories, Nutley, NJ.


28 "Product Information. Levoleucovorin (levoleucovorin)." Spectrum Chemical, Gardena, CA.


30 "Product Information. Wellcovorin (leucovorin)." Glaxo Wellcome, Research Triangle Park, NC.


33 Furlanut M, Benetello P, Avogaro A, Dainese R "Effects of folic acid on phenytoin kinetics in


Canadian Pharmacists Association "e-CPS. Available from: URL: http://www.pharmacists.ca/function/Subscriptions/ecps.cfm?link=eCPS_quikLink."


L-METHYL-B6-B12
levomefolate calcium, pyridoxal phosphate anhydrous, and methylcobalamin tablet, coated

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**Labeler** - Virtus Pharmaceuticals OpCo II (969483143)

Revised: 2/2016