L-METHYL-B6-B12 Tablets is an orally administered medical food for the dietary management of endothelial dysfunction in patients with diabetic peripheral neuropathy.

Description

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

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), Lmethylolate Calcium, Magnesium Stearate, Methylcobalamin, and Carnauba Wax.

L-Methyl-B6-B12 Tablets do not contain sugar, lactose, yeast or gluten.

Pharmacology

*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.

*Pyridoxal-5'-phosphate (PLP)* is the active form of vitamin B6 and is used as the prosthetic group for many of the enzymes where this vitamin is involved. PLP is readily absorbed by the intestine by a process which is preceded by dephosphorylation to form pyridoxal. The phosphate group is regained during passage through the intestine. Pyridoxine, the parent compound of PLP and the most frequently used form of vitamin B6, requires reduction and phosphorylation before becoming biologically active. The PLP in L-Methyl-B6-B12 Tablets contains 25mg of pyridoxal (the active component of PLP).

*Methylcobalamin (Methyl-B12)* is one of the two forms of biologically active vitamin B12. Methyl-B12 is the principal form of circulating vitamin B12, hence the form which is transported into peripheral tissue. Methyl-B12 is absorbed by the intestine by a specific mechanism which uses the intrinsic factor and by a diffusion process in which approximately 1% of the ingested dose is absorbed. Cyanocobalamin and hydroxycobalamin are forms of the vitamin that require conversion to methylcobalamin.

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 halflife is approximately 3 hours for Lmethylfolate after the administration of 5mg of oral D,L-methylfolate. The mean values for $C_{\text{max}}$, $T_{\text{max}}$, 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. Plasma protein binding studies showed that L-methylfolate is 56% bound to plasma proteins.

Indication and Usage

L-Methyl-B6-B12 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.

L-Methyl-B6-B12 Tablets are indicated for the distinct nutritional requirements of patients with endothelial dysfunction and/or hyperhomocysteinemia who present with lower extremity ulceration(s).

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

Contraindications

There have been rare reports of hypersensitivity (allergic-like reactions) to L-Methyl-B6-B12 Tablets. Therefore, a known hypersensitivity to any of the components in the product is a contraindication to its use for any indication.

Precautions

General

Folic acid, when administered as a single agent in doses above 0.1mg daily, 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. Folate therapy alone is inadequate for the treatment of a B$_{12}$ deficiency.

Patient Information

L-Methyl-B6-B12 Tablets is a medical food to be used only under medical supervision.

Drug Interactions

L-Methyl-B6-B12 Tablets 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). This may possibly reduce first generation anticonvulsants effectiveness and/or increase the frequency of seizures in susceptible patients. While the concurrent use of folic acid and first
generation anticonvulsants or pyrimethamine may result in decreased efficacy of anticonvulsants, no such decreased effectiveness has been reported with the use of L-methylfolate. Nevertheless, caution should be used when prescribing L-Methyl-B6-B12 Tablets among patients who are receiving treatment with first generation anticonvulsants or pyrimethamine. Pyridoxal 5'-phosphate should not be given to patients receiving the drug levodopa, because the action of levodopa is antagonized by pyridoxal 5'-phosphate. However, pyridoxal 5'-phosphate may be used concurrently in patients receiving a preparation containing both carbiprod and levodopa. Capecitabine (Xeloda®) toxicity may increase with the addition of leucovorin (5-formyltetrahydrofolate) (folate).

Drugs added to L-Methyl-B6- B12 Tablets

Antibiotics may alter the intestinal microflora and may decrease the absorption of methylcobalamin. Cholestyramine, colchicines or colestipol may decrease the enterohepatic reabsorption of methylcobalamin. Metformin, para-aminosalicylic acid and potassium chloride may decrease the absorption of methylcobalamin. Nitrous oxide can produce a functional methylcobalamin deficiency. Several drugs are associated with lowering serum folate levels or reducing the amount of active folate available. First generation anticonvulsants (carbamazepine, fosphenytoin, phenytoin, phenobarbital, primidone, valproic acid, valproate)23,24 and lamotrigine25 (a second-generation anticonvulsant) may decrease folate plasma levels. Information on other second-generation anticonvulsants impact on folate levels is limited and cannot be ruled out. Diavalproex sodium,26 topiramate,27 gabapentin,28 pregabalin,29 levetiracetam,30 tiagabine,31 zonisamide,32 have not reported the potential to lower folate in their respective prescribing information. Methotrexate, alcohol (in excess), sulfasalazine, cholestyramine, colchicine, colestipol, L-dopa, methylprednisone, NSAIDs (high dose), pancreatic enzymes (pancrelipase, pancratin), pentamidine, pyrimethamine, smoking, triamterene, and trimethoprim may decrease folate plasma levels. 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 L-Methylfolate Calcium. 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. L-Methyl-B6-B12 Tablets must be used under medical supervision.

How Supplied

L-Methyl-B6-B12 Tablets 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 ninety (90) tablets.

Commercial Product (90 tablets)
76439-362-90

Use under medical/physician supervision.

1 Virtus Pharmaceuticals, LLC does not represent this product code to be a National Drug Code (NDC) number. Instead, Virtus Pharmaceuticals, LLC has assigned a product code formatted 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 (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. 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


Boykin J. V. Jr., Ischemic Vascular Disease, Nitric Oxide Deficiency, and Impaired Wound Healing. Vascular Disease Management 2007; 2(1) 1-8.


United States Food and Drug Administration Title 21 Code of federal Regulations 101.9(j)(8).


Leucovorin Calcium (folinic acid) For Injection Prescribing Information: December 2003; Mayne Pharma (USA) Inc.

Lamictal® (lamotrigine) Prescribing Information: August 2005; Glaxo-SmithKline.

Depakote® (divalproex sodium) Prescribing Information: January 2006; Abbott Laboratories.

Topamax® (topiramate) Prescribing Information: June 2005; ORTHO-McNEIL NEUROLOGICS, INC.

Neurontin® (gabapentin) Prescribing Information: December 2005; Parke-Davis.

Lyrica® (pregabalin) Prescribing Information: March 2006; Parke- Davis.

Keppra® (levetiracetam) Prescribing Information: March 2007; UCB, Inc.

Gabitril (tiagabine) Prescribing Information: March 2005: Cephalon, Inc.

Zonegran® (zonisamide) Prescribing Information: December 2004: Elan Pharma International Ltd.;
L-METHYL-B6-B12
levomefolate calcium, pyridoxal phosphate anhydrous, and methylcobalamin tablet, coated

**Product Information**

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**Product Information**

- **Product Type**: MEDICAL FOOD
- **Item Code (Source)**: NHRIC:76439-362
- **Route of Administration**: ORAL

**Active Ingredient/Active Moiety**

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**Labeler** - Virtus Pharmaceuticals (969483143)

Revised: 1/2015