

CEREFOLIN® Tablets

A medical food for the dietary management of hyperhomocysteinemia.

Description

Each round coated blue colored tablet contains:

Dietary Ingredients:

L-methylfolate Calcium (as Metafolin®)* .6 mg
Riboflavin..... 5 mg
Pyridoxine (as Pyridoxine HCl)..... 50 mg
Cyanocobalamin 1 mg

*CAS#129025-21-4

Ingredients:

Microcrystalline Cellulose, Pyridoxine HCl, Opadry II Blue #40L10890 (Polydextrose, Hypromellose HPMC 2910, Titanium dioxide, Triacetin, FD&C Blue # 1 aluminum lake, PEG 800), Stearic Acid (Vegetable Source), Croscarmellose Sodium, L-methylfolate Calcium, Riboflavin, Silicon Dioxide, Magnesium Stearate (Vegetable Source), Opadry II Clear #Y-19-7483, (Hypromellose HPMC 2910, PEG 400, Maltodextrin), Cyanocobalamin.

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 0.056 milligrams of D-methylfolate in Cerefolin.

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

Indication and Usage

CEREFOLIN® tablets are indicated for the distinct nutritional requirements of individuals under medical supervision for hyperhomocysteinemia; with particular emphasis for individuals diagnosed with or at risk for mild to moderate: cognitive impairment¹, vascular dementia², or Alzheimer's disease³.

Precautions

Folates, when administered as a single agent in doses above 0.1mg daily, may obscure pernicious anemia in that hematologic remission can occur while neurological manifestations remain progressive. The 1 mg of cyanocobalamin contained in CEREFOLIN® has been shown to provide an adequate amount of cyanocobalamin to address this precaution⁴. A safe upper limit of 100 mg per day has been established for the unsupervised medical use of pyridoxine. Consider all sources of pyridoxine supplementation when prescribing CEREFOLIN®.

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 Metafolin®. Paresthesia, somnolence, nausea and headaches have been reported with pyridoxine. Mild transient diarrhea, polycythemia vera, itching, transitory exanthema and the feeling of swelling of the entire body has been associated with cyanocobalamin. Transient headaches have been reported infrequently with the use of CEREFOLIN®. If headaches should occur with the use of CEREFOLIN® consult with your medical practitioner.

Contraindications

Known hypersensitivity to any of the components in the product is a contraindication.

Drug Interactions

CEREFOLIN® 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 increasing 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 CEREFOLIN® among patients who are receiving treatment with first generation anticonvulsants or pyrimethamine. Pyridoxine should not be given to patients receiving the drug levodopa, because the action of levodopa is antagonized by pyridoxine. However, pyridoxine may be used concurrently in patients receiving a preparation containing both carbidopa and levodopa. Capecitabine (Xeloda®) toxicity may increase with the addition of leucovorin (5-formyltetrahydrofolate) (folate).

MERCK EXHIBIT 2257

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Drugs added to **CEREFOLIN™**: Antibiotics may alter the intestinal microflora and may decrease the absorption of cyanocobalamin. Cholestyramine, colchicines or colestipol may decrease the enterohepatic reabsorption of cyanocobalamin. Metformin, para-aminosalicylic acid and potassium chloride may decrease the absorption of cyanocobalamin. Nitrous oxide can produce a functional cyanocobalamin 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) and lamotrigine (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. 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.

Patient Information

CEREFOLIN® is a medical food for use only under medical supervision.

Dosage and Administration

Usual adult dose is one to two tablets daily or as directed by your medical practitioner. **CEREFOLIN®** is not recommended for use with children under the age of twelve.

How Supplied

Available as a round coated blue colored tablet. Debossed with "PAL" on one side and "M5" on the other. Commercial product is supplied in bottles of 90 tablets. Use under medical/physician supervision.

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 0525-0503-90*) in original light-resistant container.

*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.

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 Lehmann M, Regland B, Blennow K, and Gottfries CG: Vitamin B12-B6-Folate Treatment Improves Blood-Brain Barrier Function in Patients with Hyperhomocysteinaemia and Mild Cognitive Impairment. *Dementia and Geriatric Cognitive Disorders* 2003;16:145-150.
- 2 Nilsson K, Gustafson L, and Hultberg B: Improvement of cognitive functions after cobalamin/folate supplementation in elderly patients with dementia and elevated plasma homocysteine. *International Journal of Geriatric Psychiatry* 2001;16:609-614.
- 3 Seshadri S, Beiser A, Selhub J, Jacques PF, Rosenberg IH, D'Agostino RB, Wilson PWF, and Wolf PA: Plasma Homocysteine As A Risk Factor For Dementia And Alzheimer's Disease. *New England Journal of Medicine* 2002;Vol346, No. 7:476-483.
- 4 Lederle FA: Oral cobalamin for pernicious anaemia: medicine's best kept secret? *JAMA* 1991;265:94-95.

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Distributed By

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