CerefolinNAC® Caplets

DESCRIPTION

CerefolinNAC® is an orally administered medical food for use only under medical supervision for the dietary management of certain metabolic processes identified with early memory loss.

Each oval coated blue colored caplet contains:

Dietary Ingredients:

L-methylfolate Calcium (as Metafolin®)*	6 mg
Methylcobalamin	2 mg
N-Acetylcysteine	600 mg

*CAS#151533-22-1

Ingredients:

N-acetylcysteine, Microcrystalline Cellulose, Opadry II Blue 07F90856 (Hypromellose, Talc, Titanium Dioxide, Polyethylene Glycol, FD&C Blue #2-Aluminum Lake, Saccharin Sodium), and Magnesium Stearate (Vegetable Source), L-methylfolate Calcium, Methylcobalamin.

CerefolinNAC® caplets 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 isomer of folate[1] and the 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 the cell, 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]. Certain 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 0.06 milligrams of D-methylfolate in CerefolinNAC®.

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]

Methylcobalamin (Methyl-B_{12}) is one of two forms of biologically active vitamin B_{12}. Methyl-B_{12} is the principal form of circulating vitamin B_{12}, hence the form which is transported into peripheral tissue. Methyl-B_{12} is absorbed by a specific intestinal mechanism which uses 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 Methyl-B_{12} via the intermediate glutathionyl- B_{12}.

N-acetylcysteine (NAC) is a precursor to glutathione (GSH) one of the body's most potent natural antioxidants. NAC is converted to GSH intracellularly. The presence of appropriate amounts of intracellular GSH helps to maintain the ability of the neurovascular tissue to metabolize vitamin B_{12} and to reduce or eliminate oxidative stress in these tissues. NAC significantly lowers plasma homocysteine concentrations[10,11], and increases total antioxidant capacity (TAC)[12], thus correcting the characteristic pattern of changes in cognitively impaired patients with hyperhomocysteinemia [13,14,15].

Pharmacokinetics[9,16]:

Absorption and Elimination: L-methylfolate is a water soluble molecule which is primarily excreted via the kidneys[16]. 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 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 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[16]. Plasma protein binding studies showed that L-methylfolate is 56% bound to plasma proteins[9].

INDICATIONS AND USAGE

CerefolinNAC® is indicated for the distinct nutritional requirements of individuals under treatment for early memory loss[26] with particular emphasis for those individuals diagnosed with or at risk for neurovascular oxidative stress[15,17,18] and/or hyperhomocysteinemia[19]; mild to moderate cognitive impairment with or without vitamin B_{12} deficiency[10,14,20], vascular dementia[13,14,21] or Alzheimer's disease[13,14,17,22].

CerefolinNAC® should always be used under medical supervision.

CONTRAINDICATIONS

There have been rare reports of hypersensitivity (allergic-like reactions) to **CerefolinNAC®.** Therefore, a known hypersensitivity to any 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[23,24]. Folate therapy alone is inadequate for the treatment of a B_{12} deficiency. The 2 mg of methylcobalamin contained in **CerefolinNAC®** has been shown to provide an adequate amount of cobalamin to address this precaution[25]. NAC should be avoided by nursing mothers. NAC clearance is reduced in those with chronic liver disease as well as in pre-term newborns. Headaches may be intensified in those taking NAC and nitrates for the treatment of angina. While the incidence of renal stones is low, those that do form renal stones, particularly cysteine stones should avoid **CerefolinNAC®**. Do not administer **CerefolinNAC®** to critically ill patients. NAC and its sulfhydryl metabolites could produce a false-positive result in the nitroprusside test for ketone bodies used in diabetes. **CerefolinNAC®** should be used with caution in those with a history of peptic ulcer disease since NAC may disrupt the gastric mucosal barrier.

Patient Information:

CerefolinNAC® is a medical food[27] for use only under medical supervision and direction.

Drug Interactions;

CerefolinNAC®*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).[28,29] This may possibly reduce first generation anticonvulsants effectiveness and/or increase the frequency of seizures in susceptible patients.[28,29] 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 6(S)-5-Methyltetrahydrofolic acid (as L-methylfolate; Metafolin®). Nevertheless, caution should be used when prescribing **CerefolinNAC®** 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 carbidopa and levodopa. Capecitabine (Xeloda®) toxicity may increase with the addition of leucovorin (5-formyltetrahydrofolate) (folate).

Drugs added to* CerefolinNAC®*: 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. 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)[28,29] and lamotrigine[30] (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,[31] topiramate,[32] gabapentin,[33] pregabalin,[34] levetiracetam,[35] tiagabine,[36] zonisamide,[37] 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 oral L-methylfolate. Mild transient diarrhea, polycythemia vera, itching, transitory exanthema and the feeling of swelling of the entire body have been associated with methylcobalamin. Nausea, vomiting, headache, other gastrointestinal symptoms, and rash (with or without mild fever) have been associated with NAC. There are rare reports of renal stone formation with NAC.

DOSAGE AND ADMINISTRATION

Usual adult dose is one caplet daily under medical supervision. **CerefolinNAC®** is not recommended for use with children under the age of twelve.

CerefolinNAC® must be administered under medical supervision.

HOW SUPPLIED

Available as an oval coated blue colored caplet. Debossed with "PAL" on one side and "600" on the other. Commercial product is supplied in bottles of 90 caplets. Sample product is supplied in a bottle containing three caplets.

Commercial Product (90 caplets)	0525-0510-90*	Use under medical/physician supervision.
Sample Product Bottle (3 caplets)	0525-0510-03*	Professional Samples – Not for sale.

*Pamlab LLC does not represent these product codes to 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 heat, light and moisture.

PATENTS

Some or all of the following patents may apply:

U.S. Patent No. 5,563,126	U.S. Patent No. 6,254,904
U.S. Patent No. 5,795,873	U.S. Patent No. 6,297,224
U.S. Patent No. 5,997,915	U.S. Patent No. 6,528,496
U.S. Patent No. 6,011,040	U.S. Patent No. 7,709,460
U.S. Patent No. 6,207,651	and other pending patent applications.

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[37] Zonegran® (zonisamide) Prescribing Information: December 2004: Elan Pharma International Ltd.; licensed to Eisai Inc

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PAMLAB, L.L.C. Covington, LA 70433 Revised 4/10
PC-0060-03