

**L-METHYL-MC-NAC - levomefolate calcium, methylcobalamin, and acetylcysteine tablet, coated**  
**AvKARE, Inc.**

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**L-Methyl-MC-NAC Tablets**

**DESCRIPTION**

**L-Methyl-MC-NAC Tablets** is an orally administered prescription medical food 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	6 mg
Methylcobalamin	2 mg
N-Acetylcysteine	600 mg

**Ingredients**

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

**L-Methyl-MC-NAC** 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 isomer of folate <sup>1</sup> and the form of folate in circulation <sup>2</sup>. It is also the form which is transported across membranes into peripheral tissues <sup>3</sup>, particularly across the blood brain barrier <sup>4</sup>. In the cell, 6(S)-5-MTHF is used in the methylation of homocysteine to form methionine and tetrahydrofolate (THF) <sup>1</sup>. THF is the immediate acceptor of one carbon units for the synthesis of thymidine-DNA, purines (RNA and DNA) and methionine <sup>5</sup>. Folic acid, the synthetic form of folate, must undergo enzymatic reduction by methylenetetrahydrofolate reductase (MTHFR) to become biologically active <sup>6</sup>. Certain genetic mutations of MTHFR result in a cell's inability to convert folic acid to 6(S)-5-MTHF <sup>7</sup>.

*Methylcobalamin (Methyl-B<sub>12</sub>)* is one of two forms of biologically active vitamin B<sub>12</sub>. Methyl-B<sub>12</sub> is the principal form of circulating vitamin B<sub>12</sub>, hence the form which is transported into peripheral tissue. Methyl-B<sub>12</sub> 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<sub>12</sub> via the intermediate glutathionyl- B<sub>12</sub>.

*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<sub>12</sub> and to reduce or eliminate oxidative stress in these tissues. NAC significantly lowers plasma homocysteine concentrations<sup>9,10</sup>, and increases total antioxidant capacity (TAC)<sup>11</sup>, thus correcting the characteristic pattern of changes in cognitively impaired patients with hyperhomocysteinemia <sup>12,13,14</sup>.

**Pharmacokinetics** <sup>8,15</sup>

## Absorption and Elimination

L-methylfolate is a water soluble molecule which is primarily excreted via the kidneys<sup>15</sup>. In a study of subjects with coronary artery disease (n=21), peak plasma levels were reached in 1-3 hours following ORAL/PARENTERAL administration<sup>8</sup>. Peak concentrations of L-methylfolate were found to be more than seven times higher than folic acid (129 ng ml<sup>-1</sup> vs. 14.1 ng ml<sup>-1</sup>) 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<sub>max</sub>, T<sub>max</sub>, and AUC<sub>0-12</sub> were 129 ng ml<sup>-1</sup>, 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<sup>15</sup>. Plasma protein binding studies showed that L-methylfolate is 56% bound to plasma proteins<sup>8</sup>.

## INDICATIONS AND USAGE

**L-Methyl-MC-NAC** Tablets is indicated for the distinct nutritional requirements of individuals under a physician's treatment for early memory loss<sup>25</sup> with particular emphasis for those individuals diagnosed with or at risk for neurovascular oxidative stress<sup>14,16,18</sup> and/or hyperhomocysteinemia<sup>18</sup>; mild to moderate cognitive impairment with or without vitamin B<sub>12</sub> deficiency<sup>9,13,19</sup>, vascular dementia<sup>12,13,21</sup> or Alzheimer's disease<sup>12,13,16,21</sup>.

**L-Methyl-MC-NAC** Tablets should always be used under medical supervision.

## CONTRAINDICATIONS

There have been rare reports of hypersensitivity (allergic-like reactions) to **L-Methyl-MC-NAC** Tablets. 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 0.1 mg daily, may obscure the detection of B<sub>12</sub> deficiency (specifically, the administration of folic acid may reverse the hematological manifestations of B<sub>12</sub> deficiency, including pernicious anemia, while not addressing the neurological manifestations). L-methylfolate may be less likely than folic acid to mask vitamin B<sub>12</sub> deficiency<sup>22,23</sup>. Folate therapy alone is inadequate for the treatment of a B<sub>12</sub> deficiency. The 2 mg of methylcobalamin contained in **L-Methyl-MC-NAC** Tablets has been shown to provide an adequate amount of cobalamin to address this precaution<sup>24</sup>. 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 **L-Methyl-MC-NAC** Tablets. Do not administer **L-Methyl-MC-NAC** Tablets 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. **L-Methyl-MC-NAC** Tablets should be used with caution in those with a history of peptic ulcer disease since NAC may disrupt the gastric mucosal barrier.

### Patient Information

**L-Methyl-MC-NAC** Tablets is a medical food<sup>26</sup> for use only under medical supervision and direction.

### Drug Interactions

## L-Methyl-MC-NAC 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).<sup>27,28</sup> This may possibly reduce first generation anticonvulsants effectiveness and/or increase the frequency of seizures in susceptible patients.<sup>27,28</sup> 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). Nevertheless, caution should be used when prescribing **L-Methyl-MC-NAC** 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 carbidopa and levodopa. Capecitabine (Xeloda<sup>®</sup>) toxicity may increase with the addition of leucovorin (5-formyltetrahydrofolate) (folate).

## Drugs added to L-Methyl-MC-NAC Tablets

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, paraaminosalicylic 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, phenobarbital, primidone, valproic acid, valproate)<sup>27,28</sup> and lamotrigine<sup>30</sup> (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. Divalproex sodium,<sup>30</sup> topiramate,<sup>31</sup> gabapentin,<sup>32</sup> pregabalin,<sup>33</sup> levetiracetam,<sup>34</sup> tiagabine,<sup>35</sup> zonisamide,<sup>36</sup> 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.

**To report SUSPECTED ADVERSE REACTIONS contact AvKARE, Inc. at 1-855-361-3993; email [drugsafety@avkare.com](mailto:drugsafety@avkare.com); or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

## DOSAGE AND ADMINISTRATION

Usual adult dose is one caplet daily under medical supervision.

**L-Methyl-MC-NAC** Tablets is not recommended for use with children under the age of twelve.

**L-Methyl-MC-NAC** Tablets must be administered under medical supervision.

## HOW SUPPLIED

Available as an oval coated blue colored caplet. Debossed with "V361" on one side and blank on the other. Supplied in bottles of 90 caplets (NDC 42291-362-90).

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.

### **PATENTS**

Some or all of the following patents may apply:

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**

<sup>1</sup> Donaldson, K. and K. JC., Naturally occurring forms of folic acid. II. Enzymatic conversion of methylenetetrahydrofolic acid to prefolate A-methyltetrahydrofolate. *J Biol Chem*, 1962. 237: p. 1298-304.

<sup>2</sup> Sweeney, M.R., J. McPartlin, and J. Scott, Folic acid fortification and public health: report on threshold doses above which unmetabolised folic acid appear in serum. *BMC Public Health*, 2007. 7: p. 41

<sup>3</sup> Wagner, C., Cellular folate binding proteins; function and significance. *Annu Rev Nutr*, 1982. 2: p. 229-48.

<sup>4</sup> Spector, R. and A.V. Lorenzo, Folate transport in the central nervous system. *Am J Physiol*, 1975. 229(3): p. 777-82.

<sup>5</sup> Selhub, J., Folate, vitamin B<sub>12</sub> and vitamin B<sub>6</sub> and one carbon metabolism. *J Nutr Health Aging*, 2002. 6(1): p. 39-42.

<sup>6</sup> Wright, A.J., J.R. Dainty, and P.M. Finglas, Folic acid metabolism in human subjects revisited: potential implications for proposed mandatory folic acid fortification in the UK. *Br J Nutr*, 2007: p. 1-9.

<sup>7</sup> Chen, Z., A.C. Karaplis, S.L. Ackerman, I.P. Pogribny, S. Melnyk, S. Lussier-Cacan, M.F. Chen, A. Pai, S.W. John, R.S. Smith, T. Bottiglieri, P. Bagley, J. Selhub, M.A. Rudnicki, S.J. James, and R. Rozen, Mice deficient in methylenetetrahydrofolate reductase exhibit hyperhomocysteinemia and decreased methylation capacity, with neuropathology and aortic lipid deposition. *Hum Mol Genet*, 2001. 10(5): p. 433-43.

<sup>8</sup> Willems FF, Boers GH, Blom HJ, et al. Pharmacokinetic Study on the Utilization of 5-methyltetrahydrofolate and Folic Acid in Patients with Coronary Artery Disease. *Br J Pharmacol* 2004;141:825-830.

<sup>9</sup> Lehmann M, Regland B, Blennow K, and Gottfries CG: Vitamin B<sub>12</sub>-B<sub>6</sub>- Folate Treatment Improves Blood- Brain Barrier Function in Patients with Hyperhomocysteinemia and Mild Cognitive Impairment. *Dementia and Geriatric Cognitive Disorders* 2003; 16:145-150.

- 10 Hultberg, B., Andersson, A., Masson, P., Larson, M., and Tunek, A. Plasma Homocysteine and Thiol Compound Fractions After Oral Administration of N-Acetylcysteine. *Scand.J.Clin.Lab Invest* 1994;54(6):417-22.
- 11 Ventura, P., Panini, R., Abbati, G., Marchetti, G., and Salvioli, G. Urinary and Plasma Homocysteine and Cysteine Levels During Prolonged Oral N-Acetylcysteine Therapy. *Pharmacology* 2003;68(2):105-14.
- 12 McCaddon A and Davies G: Coadministration of N-acetylcysteine, vitamin B<sub>12</sub> and folate in cognitively impaired hyperhomocysteinaemic patients. *International Journal of Geriatric Psychiatry* 2005; 20(10):998- 1000.
- 13 McCaddon A and Davies G: Clinical effects of co-administering N-acetylcysteine, vitamin B<sub>12</sub> and folate in cognitively impaired hyperhomocysteinaemic patients. *Haematologica Reports* 2005;1(3):49-50. Poster presentation at the 5th Homocysteine Conference in Milan, Italy June 26th – June 30th 2005.
- 14 Guidi I, Galimberti D, Lonati S, Novembrino C, Bamonti F, Tiriticco M, Fenoglio C, Venturelli E, Baron P, Bresolin N and Scarpini E: Oxidative imbalance in patients with mild cognitive impairment and Alzheimer's disease. *Neurobiology of Aging* 2006; 27(2):262-269.
- 15 5-Methyltetrahydrofolate. (Monograph), *Alternative Medicine Review*, 2006. 11(4):330-337
- 16 Adair JC, Knoefel JE and Morgan N: Controlled trial of N-acetylcysteine for patients with probable Alzheimer's disease. *Neurology* 2001;57:1515-1517.
- 17 Boyd-Kimball D, Sultana R, Abdul HM and Butterfield DA:  $\gamma$ -Glutamylcysteine Ethyl Ester-Induced Up-Regulation of Glutathione Protects Neurons Against A $\beta$  (1-42)-Mediated Oxidative Stress and Neurotoxicity: Implications for Alzheimer's Disease. *Journal of Neuroscience Research* 2005;79:700-706.
- 18 Wiklund O, Fager G, Andersson A, Lundstam U, Masson P and Hultberg B: N-acetylcysteine treatment lowers plasma homocysteine but not serum lipoprotein(a) levels. *Atherosclerosis* 119 (1996) 99-106.
- 19 PDR<sup>®</sup> For Nutritional Supplements, 2001;ISBN: 1-56363-364-7: 477-86.
- 20 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.
- 21 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.
- 22 B Akoglu, M Schrott, H Bolouri, A Jaffari, E Kutschera, WF Caspary and D Faust: The Folic Acid Metabolite L-5- Methyltetrahydrofolate Effectively Reduces Total Serum Homocysteine Level in Orthotopic Liver Transplant Recipients: A Double-Blind Placebo- Controlled Study. *European Journal of Clinical Nutrition* (2007), 1–6
- 23 Scott JM, Weir DG: The Methylfolate Trap. A Physiological Response in Man to Prevent Methyl Group Deficiency in Kwashiorkor and an Explanation for Folic-Acid-Induced Exacerbation of Subacute Combined Degeneration in Pernicious Anemia; *Lancet*. 1981 2:337-340
- 24 Kuzminski AM, Del Giacco EJ, Allen RH, et al.: Effective Treatment Of Cobalamin Deficiency With Oral Cobalamin. *Blood* 1998; 92:1191- 1198.
- 25 Durga J et al. Effect of a 3 year folic acid supplementation on cognitive function in older adults in the FACIT trial; a randomized, double blind, controlled trial. *The Lancet* 2007;369:208- 216.
- 26 United States Food and Drug Administration Title 21 Code of federal Regulations 101.9(j)(8).
- 27 PDR For Nutritional Supplements, (n.19) pp. 157-67.

<sup>28</sup> Leucovorin Calcium (folinic acid) For Injection Prescribing Information: December 2003; Mayne Pharma (USA) Inc.

<sup>29</sup> Lamictal<sup>®</sup> (lamotrigine) Prescribing Information: August 2005; GlaxoSmith- Kline.

<sup>30</sup> Depakote<sup>®</sup> (Divalproex sodium) Prescribing Information: January 2006; Abbott Laboratories.

<sup>31</sup> Topamax<sup>®</sup> (topiramate) Prescribing Information: June 2005; ORTHO-McNEIL NEUROLOGICS, INC.

<sup>32</sup> Neurontin<sup>®</sup> (gabapentin) Prescribing Information: December 2005; Parke- Davis.

<sup>33</sup> Lyrica<sup>®</sup> (pregabalin) Prescribing Information: March 2006; Parke-Davis.

<sup>34</sup> Keppra<sup>®</sup> (levetiracetam) Prescribing Information: March 2007; UCB, Inc.

<sup>35</sup> Gabitril (tiagabine) Prescribing Information: March 2005; Cephalon, Inc.

<sup>36</sup> Zonegran<sup>®</sup> (zonisamide) Prescribing Information: December 2004: Elan Pharma International Ltd.; licensed to Eisai Inc

Manufactured for:

**AvKARE, Inc.**  
Pulaski, TN 38478

Mfg. Rev. 11/14

AV 04/16 (P)

## **PACKAGE LABEL.PRINCIPAL DISPLAY PANEL**

**AvKARE**

**NDC 42291-362-90**

**L-METHYL-MC NAC**

**TABLETS**

90 Tablets

Must be used under the supervision of a physician.

**Description:** Each blue colored coated caplet contains:

L-methylfolate Calcium .....	6 mg
Methylcobalamin .....	2 mg
N-Acetylcysteine .....	600 mg

### **Ingredients:**

N-Acetylcysteine, Microcrystalline, Cellulose, Opadry TM Blue 07F90856 (Hypromellose, Talc, Titanium Dioxide, Polyethylene Glycol, FD&C Blue #2-Aluminum Lake, Saccharin Sodium), Magnesium Stearate (Vegetable Source), L-methylfolate calcium, Methylcobalamin and Carnauba Wax. Sugar, lactose, yeast, and gluten free.

See package insert for complete product information.

**Identity:** L-Methyl-MC-NAC Tablets 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.

This product has been manufactured in a facility that also manufactures products containing milk and

soy. Individuals with allergic tendencies to these substances should use discretion.

**L-Methyl-MC-NAC is not recommended for use in children under the age of twelve.**

Store at controlled room temperature 15°-30°C (59°-86°F). [See USP]. Protect from light and moisture. Dispense in a tight, light-resistant container.

**If you are pregnant or nursing a baby, please ask a health professional.**

**KEEP THIS OUT OF REACH OF CHILDREN.**

All prescriptions using this product shall be pursuant to state statutes as applicable. This is not an Orange Book product.

**Call your medical practitioner about side effects.**

You may report side effects by calling 1-855-361-3993

Manufactured for:  
**AvKARE, Inc.**  
 Pulaski, TN 38478

Mfg. Rev. 11/14 AV 04/16 (P)

N3 42291 36290 1



<b>L-METHYL-MC-NAC</b>			
levomefolate calcium, methylcobalamin, and acetylcysteine tablet, coated			
<b>Product Information</b>			
<b>Product Type</b>	MEDICAL FOOD	<b>Item Code (Source)</b>	NHRIC:4229 1-362(NDC:76 439 -36 1)
<b>Route of Administration</b>	ORAL		
<b>Active Ingredient/Active Moiety</b>			
<b>Ingredient Name</b>		<b>Basis of Strength</b>	<b>Strength</b>
LEVOMEFOLATE CALCIUM (UNII: A9R10K3F2F) (LEVOMEFOLIC ACID - UNII:8S95DH25XC)		LEVOMEFOLATE CALCIUM	6 mg

<b>METHYLCOBALAMIN</b> (UNII: BR1SN1JS2W) (METHYLCOBALAMIN - UNII:BR1SN1JS2W)	METHYLCOBALAMIN	2 mg
<b>ACETYLCYSTEINE</b> (UNII: WYQ7N0BPYC) (ACETYLCYSTEINE - UNII:WYQ7N0BPYC)	ACETYLCYSTEINE	600 mg

### Inactive Ingredients

Ingredient Name	Strength
<b>CELLULOSE, MICROCRYSTALLINE</b> (UNII: OP1R32D61U)	
<b>HYPROMELLOSES</b> (UNII: 3NXW29V3WO)	
<b>TALC</b> (UNII: 7SEV7J4R1U)	
<b>TITANIUM DIOXIDE</b> (UNII: 15FIX9V2JP)	
<b>Polyethylene Glycol, Unspecified</b> (UNII: 3WJQ0SDW1A)	
<b>FD&amp;C BLUE NO. 2</b> (UNII: L06K8R7DQK)	
<b>ALUMINUM OXIDE</b> (UNII: LM26O6933)	
<b>SACCHARIN SODIUM</b> (UNII: SB8ZUX40TY)	
<b>MAGNESIUM STEARATE</b> (UNII: 70097M6I30)	
<b>CARNAUBA WAX</b> (UNII: R12CBM0EIZ)	

### Product Characteristics

<b>Color</b>	BLUE	<b>Score</b>	no score
<b>Shape</b>	OVAL	<b>Size</b>	19mm
<b>Flavor</b>		<b>Imprint Code</b>	V361
<b>Contains</b>			

### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NHRIC:42291-362-90	90 in 1 BOTTLE		

### Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
MEDICAL FOOD		06/22/2015	

**Labeler** - AvKARE, Inc. (796560394)

Revised: 4/2016

AvKARE, Inc.