Metafolbic™ Plus

DESCRIPTION

Metafolbic™ Plus is an orally administered medical food recommended for use under the supervision of a physician or health-care professional.

Each oval coated blue colored caplet contains:

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

*CAS#151533-22-1

Other Ingredients:
Microcrystalline Cellulose, Opadry™ Blue 07F90856 [color] (Hypromelloses, Talc, Titanium Dioxide [color], PEG 3350, FD&C Blue No. 2 Aluminum Lake [color], Saccharin Sodium), Magnesium Stearate (Vegetable Grade), and Carnauba Wax.

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 Metafolbic™ Plus.

INDICATIONS AND USAGE

Metafolbic™ Plus is indicated for the dietary management of individuals with distinct nutritional needs relating to hyperhomocysteinemia and/or certain cognitive impairment with or without vitamin B_{12} deficiency[1,2,3]. **Metafolbic™ Plus** is labeled as a medical food for use under the active and ongoing medical supervision of a physician or healthcare provider on a recurring basis for, among other things, instructions on their use.

Medical foods are intended for the dietary management of a patient who, because of therapeutic or chronic medical needs, has 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. This Medical Food is not subject to NDA or ANDA approval and is not an Orange Book product. Although FDA does not require a prescription for Medical Foods, this product is intended to be used under active medical supervision. This product is not eligible for government reimbursement under federal programs, but is eligible for reimbursement under state programs on a case-by-case basis. Please check with a specific state to determine proper reimbursement eligibility.

These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

Metafolbic™ Plus is a medical food[4] recommended for use under the supervision of a physician or health-care professional.

CONTRAINDICATIONS

There have been rare reports of hypersensitivity (allergic-like reactions) to **Metafolbic™ Plus**. 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. Folate therapy alone may be inadequate for the treatment of a B_{12} deficiency. N-Acetylcysteine should be avoided by nursing mothers. N-Acetylcysteine clearance may be reduced in those with chronic liver disease as well as in pre-term newborns. Headaches may be intensified in those taking N-Acetylcysteine 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 **Metafolbic™ Plus**. Do not administer **Metafolbic™ Plus** to critically ill patients. N-Acetylcysteine and its sulfhydryl metabolites could produce a false-positive result in the nitroprusside test for ketone bodies used in diabetes. **Metafolbic™ Plus** should be used with caution in those with a history of peptic ulcer disease since N-Acetylcysteine may disrupt the gastric mucosal barrier.

Patient Information:

Metafolbic™ Plus is a medical food[4] recommended for use under the supervision of a physician or health-care professional.

Drug Interactions:

Metafolbic™ Plus ***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).[5,6] This may possibly reduce first generation anticonvulsants effectiveness and/or increase the frequency of seizures in susceptible patients.[5,6] 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 with **Metafolbic™ Plus** 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 **Metafolbic™ Plus:** 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)[5,6] and lamotrigine[7] (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,[8] topiramate,[9] gabapentin,[10] pregabalin,[11] levetiracetam,[12] tiagabine,[13] zonisamide,[14] 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, pancreatin), 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 N-Acetylcysteine. There are rare reports of renal stone formation with N-Acetylcysteine.

DOSAGE AND ADMINISTRATION

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

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HOW SUPPLIED

Metafolbic™ Plus is available as oval coated blue colored caplets. Debossed with "LMF6" on one side and plain on the other side.

Bottles of 90 caplets 51991-811-90**

Use under medical/physician supervision.

**Breckenridge Pharmaceutical, Inc. does not represent these product codes to be actual National Drug Codes (NDCs). Product codes are formatted according to standard industry practice to meet the formatting requirements of pharmacy and health insurance computer systems.

Storage:

Store at 25˚C (77˚F); excursions permitted to 15˚C-30˚C (59˚F-86˚F). See USP Controlled Room Temperature. Protect from moisture and light.

PATENTS

For information on applicable patents, please visit www.bpirx.com

REFERENCES

1 Lehmann M, Regland B, Blennow K, and Gottfries CG: Vitamin B_{12}-B_6-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 McCaddon A and Davies G: Clinical effects of co-administering N-acetylcysteine, vitamin B_{12} 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.

3 PDR® For Nutritional Supplements, 2001;ISBN: 1-56363-364-7: 477-86.

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

5 PDR for Nutritional Supplements, (n.19) pp. 157-67.

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

7 Lamictal® (lamotrigine) Prescribing Information: August 2005; GlaxoSmithKline.

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

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

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

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

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

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

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

To report a serious adverse event contact: 1-800-367-3395.

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