

## NURITE ACTIVE<sup>®</sup>

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Each capsule contains:

L – Methylfolate	1 mg
Mecobalamin	1500 mcg
Pyridoxal-5'-phosphate	3 mg

### 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.

Metafolin<sup>®</sup> (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 0.03 milligrams of D-methylfolate in **Nurite Active<sup>®</sup>**.

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. 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.

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 **Nurite Active**<sup>®</sup> 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<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. Plasma protein binding studies showed that L-methylfolate is 56% bound to plasma proteins.

### **INDICATION AND USAGE**

**Nurite Active**<sup>®</sup> is indicated for the distinct nutritional requirements of individuals with endothelial dysfunction who present with loss of protective sensation<sup>5</sup> and neuropathic pain associated with diabetic peripheral neuropathy.

**Nurite Active**<sup>®</sup> is indicated for the distinct nutritional requirements of patients with endothelial dysfunction and/or hyperhomocysteinemia<sup>9</sup> who present with lower extremity ulceration(s).

### **CONTRAINDICATIONS**

**Nurite Active**<sup>®</sup> is contraindicated in patients with known hypersensitivity to any of the components contained in this product.

## PRECAUTIONS

### *General:*

Folic acid, when administered in daily doses above 0.1mg, 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 Calcium may be less likely than folic acid to mask vitamin B<sub>12</sub> deficiency. Folate therapy alone is inadequate for the treatment of a B<sub>12</sub> deficiency.

## DRUG INTERACTIONS

**Nurite Active**<sup>®</sup> 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 **Nurite Active**<sup>®</sup> 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 **Nurite Active**<sup>®</sup>: 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) 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. Diavaproex sodium, topiramate, gabapentin, pregabalin, levetiracetam, tiagabine, zonisamide, 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**

Allergic reactions have been reported following the use of oral L-methylfolate Calcium. Acne, skin reactions, allergic reactions, photosensitivity, nausea, vomiting, abdominal pain, loss of appetite, increased liver function test results, 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 usual adult dose may be taken as one capsule daily (1 capsule O.D.); or as directed under medical supervision.

### **Available as**

NURITE ACTIVE<sup>®</sup> is available as a Alu-Alu pack of 10's.

### ***Storage:***

Store at controlled room temperature 15oC to 30oC (59oF to 86oF) (See USP). Protect from heat, light and moisture.