Nuring™ Active Tablets

1. Composition

L-Methylfolate	1mg
Mecobalamin	1500 mcg
Pyridoxal 5'-phosphate	0.5mg

2. Dosage form and strength

Nuring Active is available as a Alu-Alu pack of 10

3. Clinical particulars

3.1 Therapeutic indication

Nuring Active is indicated in patients with:

- Endothelial dysfunction who present with loss of protective sensation and neuropathic pain associated with diabetic peripheral neuropathy.
- Endothelial dysfunction and/or Hyperhomocysteinemia who present with lower extremity ulceration(s).

3.2 Posology and method of administration

The usual adult dose may be taken as one tablet daily (1 tablet O.D.); or as directed under medical supervision.

3.3 Contraindication

Nuring Active tablets are contraindicated in patients with Hypersensitivity to components of the formulation.

3.4 Special warnings and precautions for use

- Folic acid, when administered in daily doses above 0.1mg, may obscure the detection of B12 deficiency (specifically, the administration of folic acid may reverse the haematological manifestations of B12 deficiency, including pernicious anaemia, while not addressing the neurological manifestations).
- L-methylfolate: Calcium may be less likely than folic acid to mask vitamin B12 deficiency.
- Folate therapy alone is inadequate for the treatment of a B12deficiency.

3.5 Drug interactions

- 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 Nuring Active® 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).
- 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. Diavalproex 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.

3.6 Use in special population

- Paediatric: Safety and effectiveness of Nuring Active tablets in paediatric patients have not been established.
- Geriatric: Safety and effectiveness of Nuring Active tablets in geriatric patients have not been established.
- Liver impairment: No data available.
- Renal failure: No data available.
- Pregnancy and lactation: Pregnancy Category: C. No data is available about distribution in breast milk.

3.7 Effects on ability to drive and use machine

Patients should be cautioned against engaging in activities requiring complete mental alertness, and motor coordination such as operating machinery until their response to Nuring active is known.

3.8 Undesirable effects

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, paraesthesia, somnolence, nausea and headaches have been reported with pyridoxal 5'-phosphate. Mild transient diarrhoea, polycythemia vera, itching, transitory exanthema and the feeling of swelling of the entire body has been associated with methylcobalamin.

3.9 Overdose

There is limited experience of overdose with Sinarest new Tablets. Initiate general symptomatic and supportive measures in all cases of overdosages where necessary.

4. Pharmacological properties

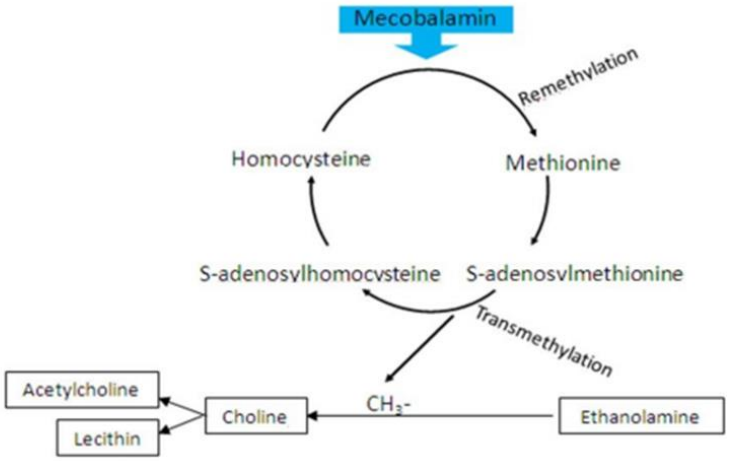
4.1 Mechanism of action

L-methylfolate is the primary biologically active isomer of folic acid and the primary form of folate in circulation. Folic acid is a precursor of tetrahydrofolic acid, which is involved as a cofactor for transformylation reactions , these reactions are involved in the biosynthesis of thymidylates and purines of nucleic acids

Mecobalamin –

- Enhances synthesis proteins in nerve cells
- promotes myelinization
- axonal regeneration

- Helps in generation of enzyme methionine synthase - regeneration of methionine from homocysteine.
- Restores diminished neurotransmitter (Acetylcholine) levels.



Pyridoxal Phosphate is a coenzyme of many enzymatic reactions. It is the active form of vitamin B6 which comprises three natural organic compounds, pyridoxal, pyridoxamine and pyridoxine. Pyridoxal phosphate acts as a coenzyme in all transamination reactions, and in some decarboxylation and deamination reactions of amino acids. The aldehyde group of pyridoxal phosphate forms a Schiff-base linkage with the epsilon-amino group of a specific lysine group of the aminotransferase enzyme. The alpha-amino group of the amino acid substrate displaces the epsilon-amino group of the active-site lysine residue. The resulting aldimine becomes deprotonated to become a quinoid intermediate, which in turn accepts a proton at a different position to become a ketimine. The resulting ketimine is hydrolysed so that the amino group remains on the protein complex.

4.2 Pharmacodynamic properties

Mecobalamin as a coenzyme of methionine synthetase, plays an important role in transmethylation in the synthesis of methionine from homocysteine. Mecobalamin is well transported to nerve cell organelles, and promotes nucleic acid and protein synthesis. Experiments in rats show that mecobalamin is better transported to nerve cell organelles than cyanocobalamin and promotes nucleic acid and protein synthesis more than cobamamide does. Experiments with cells from the brain origin and spinal nerve cells in rats also show mecobalamin to be involved in the synthesis of thymidine from deoxyuridine, promotion of deposited folic acid utilization and metabolism of nucleic acid. It promotes axonal transport and axonal regeneration. It exhibits neuropathologically and electrophysiologically inhibitory effects on nerve degeneration in neuropathies induced by drugs, such as adriamycin, acrylamide, and vincristine (in rats and rabbits), models of axonal degeneration in mice and neuropathies in rats with spontaneous diabetes mellitus. It promotes the synthesis of lecithin which is the main constituent of medullary sheath lipid. It also increases myelination of neurons in rat tissue culture more than cobamamide does. It

restores delayed synaptic transmission and diminished neurotransmitters back to normal. It promotes the maturation and division of erythroblasts, thereby alleviating anaemia. It brings about a rapid recovery of diminished red blood cell, haemoglobin, and haematocrit in vitamin B-12 deficient animals.

The two major forms of vitamin B6 are pyridoxine and pyridoxamine. In the liver they are converted to pyridoxal phosphate (PLP) which is a cofactor in many reactions of amino acid metabolism. PLP also is necessary for the enzymatic reaction governing the release of glucose from glycogen. Pyroluria is one potential cause of vitamin B6 deficiency.

4.3 Pharmacokinetic properties

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-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 Cmax, Tmax, and AUC0-12 were 129 ng ml-1, 1.3 hr., and 383 respectively. 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.

Mecobalamin substances bind to intrinsic factor; a glycoprotein secreted by the gastric mucosa, and are then actively absorbed from the gastrointestinal tract. Absorption is impaired in patients with an absence of intrinsic factor, with a malabsorption syndrome or with disease or abnormality of the gut, or after gastrectomy. Absorption from the gastrointestinal tract can also occur by passive diffusion; little of the vitamin present in food is absorbed in this manner although the process becomes increasingly important with larger amounts such as those used therapeutically. After intranasal dosage, peak plasma concentrations of cyanocobalamin have been reached in 1 to 2 hours. The bioavailability of the intranasal preparation is about 7 to 11% of that by intramuscular injection. Mecobalamin is extensively bound to specific plasma proteins called transcobalamins; transcobalamin II appears to be involved in the rapid transport of the cobalamins to tissues. Mecobalamin is stored in the liver, excreted in the bile, and undergoes extensive enterohepatic recycling; part of a dose is excreted in the urine, most of it in the first 8 hours; urinary excretion, however, accounts for only a small fraction in the reduction of total body stores acquired by dietary means. Mecobalamin diffuses across the placenta and also appears in breast milk.

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.

5. Nonclinical properties

5.1 Animal Toxicology or Pharmacology

Not required.

6. Description

Already mentioned and covered in the above points.

7. Pharmaceutical particulars

7.1 Incompatibilities

There are no known incompatibilities.

7.2 Shelf-life

24 months.

7.3 Storage and handling instructions

Store at controlled room temperature 15^{o}C to 30^{o}C . Protect from heat, light and moisture.