PRESCRIBING INFORMATION

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NEUROBION FORTE TABLETS

Tablets of Vitamin B Complex with Vit B12

Description:

Neurobion Forte Tablets is a combination of Vitamin B Complex and is indicated for use in supplementation for overall health and vitality, for healthy nervous system & general debility and weakness requiring Vitamin B complex.

Composition:

Each film coated tablet contains:

Thiamine Mononitrate IP	...10 mg
Riboflavin IP	...10 mg
Pyridoxine Hydrochloride IP	...3 mg
Cyanocobalamin triturate in Gelatine equivalent to	
Cyanocobalamin IP	...15 mcg
Nicotinamide IP	...45 mg
Calcium Pantothenate IP	...50 mg

Appropriate overages added

Colours used: Ponceau 4R Lake and Titanium Dioxide IP

List of Excipients:

Dibasic Calcium Phosphate

Disodium Edetate

Magnesium Stearate

Starch

Talc

Opadry

Properties

Pharmacology

Vitamin B complex group includes thiamine, riboflavin, nicotinic acid, pantothenic acid and cyanocobalamin.

Pharmacodynamics:

Thiamine (Vitamin B_1)

This was the first member of the B complex series identified chemically, and hence the designation, Vitamin B_1. Thiamine pyrophosphate, the physiologically active form of vitamin, constitutes the prosthetic group of the decarboxylases involved in the metabolism of pyruvic and alpha-ketoglutaric acids and thus plays an important role in the intermediary carbohydrate metabolism. Thiamine, as thiamine pyrophosphate, plays an important role in the metabolism of both carbohydrate and the branched-chain amino acids. It is a coenzyme for pyruvate dehydrogenase (lipoamide), which catalyses the conversion of pyruvate to acetyl CoA. Thiamine is also a coenzyme for oxoglutarate dehydrogenase (lipoamide), an enzyme responsible for the formation of succinyl CoA in the tricarboxylic acid cycle, and for branched-chain decarboxylase, an enzyme responsible for the catabolism of the branched-chain amino acids.2 In the body, particularly high concentrations of thiamine are found in skeletal muscles and in the heart, liver, kidney, and brain. Proper functioning of thiamine–using enzymes is required for numerous critical biochemical reactions in the body, including the synthesis of neurotransmitters; production of nucleic acids; and production of fatty acids, steroids, and certain complex sugar molecules. Thiamine deficiency produces a symptom complex with characteristic neuropathy termed beriberi. Beriberi occurs in three main forms: Wet beriberi, infantile beriberi and dry beriberi. Even though neuropathy in some form is common to all the three varieties, it is the most important manifestation in dry beriberi, while nervousness, increased irritability and depression may occur in all the three types. Wernick's encephalopathy, characterised by confusion, opthalmoplegia, nystagmus, tremors and often peripheral neuropathy, occurs due to severe thiamine deficiency. Certain symptoms of Korsakoff's psychosis encountered in chronic alcoholics and also neuritis in pregnancy and pellagra are due to thiamine deficiency. Vague symptoms like epigastric pain, anorexia, flatulence, constipation and lethargy or easy fatigability are also attributed to thiamine deficiency. In addition, inadequate functioning of the thiamine–using enzymes can interfere with the body's defence against the damage (i.e., oxidative stress) caused by harmful, highly reactive oxygen molecules called free radicals. The daily thiamine requirement is believed to be between 1.2 mg.

Riboflavin (Vitamin B_2)

The daily riboflavin requirement in an adult is 1.4 to 1.6 mg. The physiologically active form of riboflavin is formed by phosphorylation. The two coenzymes Flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), which contain this active form, play an important role in transfer of hydrogen and in oxidation of carbohydrates, amino acids and other products of metabolism. Riboflavin deficiency in man results in a syndrome characterised by angular stomatitis, glossitis, a peculiar magenta pigmentation of the tongue, cheilosis (loss of epithelium at the mucocutaneous junction of lips resulting in reddened, shiny and denuded lips); the other features are seborrheic follicular keratosis of

the nasolabial folds, nose and forehead, dermatitis of the ano-genital region and "burning feet". Certain ocular manifestations such as conjunctivitis, blepharospasm, photophobia, burning, lacrimation and vascularisation of the cornea leading to diminution in visual acuity are seen in a large proportion of cases.

Nicotinamide (Vitamin B_3)

Niacin has fundamental roles as part of reduction/oxidation of coenzymes involved in energy metabolism, amino acid metabolism, and detoxification reactions for drugs and other substances. Niacin, also known as pellagra preventing factor (PPF), is a simple organic acid. Its amide, nicotinamide, is also as effective in the treatment of pellagra. The normal daily requirement is 16 -18 mg. Nicotinic acid as nicotinamide adenine dinucleotide (NAD) and its phosphate (NADP) is the constituent of a number of co-enzymes involved in the metabolism of proteins necessary for cellular respiration. Pellagra, a symptom complex due to deficiency of nicotinic acid, occurs in endemically in individuals subsisting mainly on a diet of maize. The latter has poor nicotinic acid and tryptophan content. Non-endemic pellagra occurs in chronic alcoholism, mal-absorption syndrome, carcinoid syndrome, liver cirrhosis, poorly controlled diabetes mellitus, and in cachexia secondary to malignancy. The characteristic features are dermatitis and pigmentation of the skin, especially in regions exposed to sunlight and at various pressure points, anorexia, lethargy, stomatitis, glossitis, diarrhoea, mental confusion (dementia) and a megaloblastic anaemia. Hallucinations and other mental abnormalities may occur and spinal cord degeneration leading to spastic paraplegia occasionally develops as a complication. Though nicotinic acid deficiency is the major cause of pellagra, evidence indicates that folic acid deficiency is probably responsible for the megaloblastic anaemia, and deficiency of riboflavin which is necessary for the conversion of tryptophan into nicotinic acid, and of pyridoxine may account for the cheilosis, stomatitis, dermatitis, vaginitis and proctitis. Nicotinamide is devoid of the lipid lowering effects of nicotinic acid.

Pantothenic acid (Vitamin B_5)

This is an organic acid which serves its physiological function by being converted into coenzyme A. The daily human requirement of pantothenic acid is estimated to be below 5 mg. Coenzyme A is involved in several fundamental biological reactions. In general, all the acetylation reactions are influenced by this enzyme. Pantothenic acid deficiency produced in human volunteers by administration of a low vitamin diet containing a pantothenic acid antagonist is characterised by fatigue, malaise, headache, somnolence, paraesthesia, nausea, occasional vomiting, abdominal cramps and flatulence.

Pyridoxine (Vitamin B_6)

Pyridoxine, pyridoxal and pyridoxamine are collectively called as vitamin B6. All the three forms are converted in the body to pyridoxal phosphate which is the physiologically active form. The daily requirement is estimated at 2 mg. Pyridoxal phosphate acts as a coenzyme for amino acid decarboxylases and transaminases. It is thus intimately involved in synthesis and degradation of biogenic amines like catecholamine's, 5-HT and other important compounds like GABA (Neurotransmitters). Vitamin B_6 deficiency may cause derangement of enzymes controlling carbohydrate metabolism resulting into abnormal glucose tolerance test (GTT). Pyridoxine deficiency in adults may lead to lesions of the skin and mouth resembling those seen in ariboflavinosis and pellagra, to peripheral neuritis and to mental changes. Convulsions and hypochromic microcytic anaemia have been observed.

Cyanocobalamin (Vitamin B_{12})

Chemically, Vitamin B_{12} belongs to the family of cobalamins which are cobalt containing carrinoid compounds. These compounds differ from each other in the groups attached to the cobalt atom. In case of cyanocobalamin, a cyanide group is attached to the cobalt atom. The minimum daily requirement of vitamin B_{12} in adults is not exactly known but is believed to be extremely small, about 1 mcg per day. Vitamin B_{12} is essential to growth, cell reproduction, haematopoiesis, nucleoprotein and myelin synthesis. Intestinal absorption of Vitamin B_{12} depends on the presence of sufficient intrinsic factor and calcium ions. Intrinsic factor deficiency causes pernicious anaemia, which may be associated with subacute combined degeneration of the spinal cord. Vitamin B_{12} is bound to intrinsic factor during transit through the stomach; separation occurs in the terminal ileum in the presence of calcium, and Vitamin B_{12} enters the mucosal cell for absorption. It is then transported by the transcobalamin binding proteins. A small amount (approximately 1% of the total amount ingested) is absorbed by simple diffusion, but this mechanism is adequate only with very large doses. Oral absorption is considered too undependable to rely on in patients with pernicious anaemia or other conditions resulting in malabsorption of Vitamin B_{12}. Cyanocobalamin is the most widely used form of Vitamin B_{12}, and has hematopoietic activity apparently identical to that of the antianaemia factor in purified liver extract. Vit B_{12} deficiency is commonly asymptomatic, can also present as megaloblastic anaemia. In serious cases, the deficiency of Vit B_{12} can potentially cause severe and irreversible damage to the nervous system, including subacute combined degeneration of spinal cord.

Pharmacokinetics:

The following pharmacokinetic data is derived from the Literature review.

The B-complex vitamins are generally readily absorbed from the GI tract. They are also widely distributed in the body tissues. Excretion is through the urine as metabolites or in the original form.

Thiamine (Vitamin B_1):

Physiological amounts are absorbed by active transport. When large doses are given orally, some passive diffusion also occurs. Limited amounts are stored in tissues. About 1 mg/day is degraded in the body, excess is rapidly excreted in urine.

Riboflavin (Vitamin B_2):

Well absorbed by active transport and phosphorylated in the intestine. Riboflavin phosphate (Flavin mononucleotide: FMN) is formed in other tissues as well. Body does not significantly store riboflavin; larger doses are excreted unchanged in urine. Thiamine and riboflavin are both synthesized by colonic bacteria but this does not become available to the host.

Niacin (Vitamin B_3):

Niacin is completely absorbed from gastrointestinal tract. Physiological amounts are metabolized in the body, while larger doses are excreted unchanged in urine. Modest amounts are stored in liver.

Pyridoxine (Vitamin B_6):

Pyridoxine, pyridoxal and pyridoxamine, all three forms of the vitamin are well absorbed from the intestine. They are oxidized in the body and excreted as pyridoxic acid. Little is stored.

Pantothenic Acid (Vitamin B_5):

It is quickly absorbed and excreted unchanged in urine with little storage.

Cyanocobalamin (Vitamin B_{12}):

Intrinsic factor (a glycoprotein, MW 60,000) secreted by stomach forms a complex with B_{12}, attaches to specific receptors present on intestinal mucosal cells and is absorbed by active carrier mediated transport. This mechanism is essential for absorption of vit B_{12} ingested in physiological amounts. However, when gross excess is taken, a small fraction is absorbed without the help of intrinsic factor.

Vit B_{12} is transported in blood in combination with a specific Beta globulin transcobalamin II (TCII). Congenital absence of TCII or presence of abnormal protein (TCI or TCIII, in liver and bone marrow

disease) may interfere with delivery of Vit B_{12} to tissues. Vit B_{12} is especially taken up by liver cells and stored; about 2/3 to 4/5 of body's content (2-8 mg) is present in liver.

Vit B_{12} is not degraded in the body. It is excreted mainly in bile (3-7 mcg/day); all but 0.5-1 mcg of this is reabsorbed – considerable enterohepatic circulation occurs. Thus, in the absence of intrinsic factor or when there is malabsorption, B12 deficiency develops much more rapidly than when it is due to nutritional deficiency. It takes 3-5 years of total absence of B_{12} in diet to deplete normal body stores.

Vit B_{12} is directly and completely absorbed after i.m. or deep s.c. injection. Normally, only traces of B_{12} are excreted in urine, but when pharmacological doses (>100 mcg) are given orally or parenterally – a large part is excreted in urine, bacause the plasma protein binding sites get saturated and free vit B_{12} is filtered at the glomerulus.

Vit B_{12} is synthesized by the colonic microflora but this is not available for absorption in man.

Indication:

- Supplementation for overall health and vitality
- Supplementation for healthy nervous system
- General debility, weakness, and other symptoms such as tingling, numbness related to B vitamin deficiency which require Vitamin B complex.

Contraindications

Contraindicated in any person who is hypersensitive to any ingredients in the formulation.

Warnings & Precautions:

Pregnancy

This formulation is not been studied in pregnant women. However, Vitamin B's are essential vitamins and requirements are increased during pregnancy. Recommended dosage by ICMR should be consumed during pregnancy.

Nursing Mothers

Dosage of vitamin B's recommended by ICMR should be consumed during lactation. However, this formulation is not been studied in lactating women.

Paediatric Use

Not suitable for use in children.

Adverse Events:

There are no adverse events (ADE's) reported.

Following safety data is derived from the Literature review.

Safety

Thiamine (Vitamin B_1)

Thiamine administered orally in recommended doses usually does not evoke any adverse effects, although rarely allergic reactions and skin irritation can occur.

Riboflavin (Vitamin B_2)

Riboflavin is generally considered safe, even at high doses. However, because doses above 10 mg per day may cause eye damage from the sun. Riboflavin does not seem to cause any serious side effects. Very high doses may cause itching, numbness, burning or prickling sensations, yellow or orange urine, and sensitivity to light.

Nicotinamide (Vitamin B_3)

Besides flushing, urticaria and pruritus, large doses of the vitamin may cause furunculosis and other skin lesions, malaise, gastrointestinal disturbances, activation of peptic ulcer, bilateral amblyopia, jaundice and impairment of liver function, decrease in glucose tolerance and hyperuricemia. Most of these effects regress on stopping the drug. Nicotinic acid has been reported to potentiate the action of vasodilator drugs.

Pantothenic acid (Vitamin B_5)

Pantothenic acid is non-toxic and does not possess any other know pharmacological actions.

Pyridoxine (Vitamin B_6)

Administration of large quantities of pyridoxine has been reported to cause peripheral sensory neuropathy and ataxia. Pyridoxine interferes with therapeutic effect of levodopa.

Cyanocobalamin (Vitamin B_{12})

Vitamin B_{12} given orally have not been shown to cause any serious adverse effects. Less serious side effects of cyanocobalamin may include; headache, dizziness, weakness, nausea, upset stomach, diarrhoea, numbness or tingling, fever, joint pain, swollen tongue, swelling, itching or rash. Hypersensitivity reaction may occur with oral administration of cyanocobalamin.

Taking any one of the B vitamins for a long period of time can result in an imbalance of other important B vitamins.

Drug Interactions
Following data is derived from the Literature review.

Thiamine (Vitamin B_1)

Digoxin -- Laboratory studies suggest that digoxin may reduce the ability of heart cells to absorb and use vitamin B_1; this may be particularly true when digoxin is combined with furosemide.

Diuretics -- Diuretics (particularly furosemide) may reduce levels of vitamin B_1 in the body. It's possible that other diuretics may have the same effect.

Phenytoin -- Some evidence suggests that some people taking phenytoin have lower levels of thiamine in their blood, and that may contribute to the side effects of the drug.

Riboflavin (Vitamin B_2)

Anticholinergic Drugs -- decrease absorption of riboflavin
Tetracycline -- Riboflavin interferes with the absorption and effectiveness of tetracycline.
Tricyclic Antidepressants -- Tricyclic antidepressants (Imipramine, Desimpramine, Amitriptyline, and Nortriptyline) may reduce levels of riboflavin in the body.
Antipsychotic Medications -- Phenothiazine's (such as chlorpromazine) may lower riboflavin levels
Doxorubicin -- Riboflavin interferes with doxorubicin. Also, doxorubicin may deplete levels of riboflavin in the body.
Methotrexate – Methotrexate can interfere with riboflavin metabolism
Phenytoin -- Phenytoin may affect riboflavin levels in the body
Probenecid -- Decrease the absorption of riboflavin from the digestive tract and increase excretion of riboflavin in the urine
Thiazide Diuretics – increase riboflavin excretion in urine

Nicotinamide (Vitamin B_3)

The clearance of primidone and carbamazepine may be reduced with the concomitant use of nicotinamide.

Pantothenic Acid (Vitamin B_5)

Tetracycline -- Vitamin B_5 interferes with the absorption and effectiveness tetracycline.

Cholinesterase inhibitors -- Vitamin B_5 may increase the effects of cholinesterase inhibitors (Donepezil, Memantine hydrochloride, Galantamine, Rivastigime) potentially leading to severe side effects.

Pyridoxine (Vitamin B_6)

Drugs that reduce levels of B_6 in the body – Cycloserine, Hydralazine, Isoniazid, Penicillamine, Theophylline

Tetracycline -- All B complex vitamins, including vitamin B_6 decrease absorption of tetracycline

Antidepressant Medications -- Taking vitamin B_6 supplements may improve the effectiveness of certain tricyclic antidepressants such as nortriptyline. Other tricyclic antidepressants include amitriptyline, desipramine and imipramine. Monoamine oxidase inhibitors (MAOIs - phenelzine and tranylcypromine) may reduce blood levels of vitamin B_6.

Chemotherapy drugs -- Vitamin B_6 may reduce certain side effects of 5-fluorouracil and doxorubicin without reducing the effectiveness of the chemotherapy.

Erythropoietin (EPO) -- Erythropoietin therapy may decrease vitamin B_6 levels in red blood cells and may require B_6 supplementation.

Levodopa (L-dopa) -- Vitamin B_6 reduces the effectiveness of levodopa. Taking vitamin B_6 along with levodopa should be done only under the strict guidance of a physician.

Phenytoin -- Vitamin B_6 reduces the effectiveness of phenytoin.

Cyanocobalamin (Vitamin B_{12})

Persons taking most antibiotics, methotrexate and pyrimethamine invalidate folic acid and Vitamin B_{12} diagnostic blood assays.

Colchicine, para-aminosalicylic acid and heavy alcohol intake for longer than two weeks may produce malabsorption of Vitamin B_{12}.

Over dosage :

Following data is derived from the Literature review.

Vitamin B-1

Thiamine generally is nontoxic.

Vitamin B-2

Vitamin B-2 (riboflavin) generally is nontoxic.

Vitamin B-3

Vitamin B-3 does not have a toxic dose established for humans. However, adverse effects such as skin flushing can occur at doses of 50 mg/day or greater. While therapeutic doses are considered to typically

range from 1,500-6,000 mg/day, these doses carry a risk of liver toxicity, especially if not titrated slowly or in the presence of any pre-existing liver disease.

Vitamin B-5

Pantothenic acid generally is nontoxic.

Vitamin B-6

Over time, 300-500 mg/day of vitamin B-6 may be neurotoxic (patients with impaired renal function may be more susceptible). The acute toxic dose has generally not been established.

Vitamin B-12

The toxic dose for vitamin B-12 is not established.

Treatment of Over dosage

Vitamins B-1, B-2, B-6 and B-12

These usually require only supportive measures.

Vitamin B-3

Provide supportive treatment as needed. Aspirin taken 30 minutes before niacin decreases the flush response.

Dosage and administration

Two tablets daily; or as directed by Physician.

Storage:

Store at or below 25°C in dry place. Protect from light and moisture.

Shelf –Life:

18 months

Presentation:

Blister strip of 30 tablets

Date of Revision:

June.2024

Marketed by:

Procter & Gamble Health Limited,

Registered office:
Ground Floor and First Floor,
P&G Plaza, Cardinal Gracious Road,
Chakala, Andheri (East), Mumbai – 400099

Manufacturer:

Please refer manufacturer address on pack.